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Hair Growth and Disorders

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Ulrike Blume-Peytavi · Antonella Tosti
David A. Whiting · Ralph M. Trüeb (Eds.)

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With 270 Figures and 85 Tables

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Preface

The ideal of lifelong beautiful hair, easy to grow or to eliminate, to pigment or to depigment, to newly create or simply to replace or rearrange, is of interest to anyone interested in hair growth and its disorders, or who has patients with hair problems.

During the past 20 years, the interest in hair growth and disorders has dramatically increased. Only 20 years ago the European Hair Research Society was founded, followed by the North American Hair Research Society and the Japanese, Korean and Australasian Research Societies. The regular meetings now held on different disciplines concerning hair reflect the worldwide interest in improving our knowledge and understanding of hair and hair growth.

This textbook is testament to that interest, and contains the latest advances and scientific knowledge from the world's leading experts in hair biology and clinical trichology. In particular it covers pigmentation, genetics, hair diagnostics, pathogenesis and treatment options, hair removal and restoration techniques. Moreover, this textbook contains unique sections on tropical dermatoses of the scalp, ethnic hair and the impact of hair in forensic investigations. The book contains a chapter devoted to natural products for hair care and treatment, as well as a chapter describing hair over the ages and in art. Also, for the first time, this textbook presents a comprehensive chapter on psychocutaneous disorders of the hair and scalp.

The textbook has three sections: (i) basic aspects of human hair growth, (ii) hair and scalp disorders, and (iii) photoepilation, surgery and hair cosmetics. Each chapter provides a synonym box, a "key features" box, a summary for the clinician, and summary tables. Graphics and clinical photographs illustrate the clinical problems and possibilities. Consequently, this textbook has a strong emphasis on visual learning.

One of the main goals in editing this textbook has been to reflect the broad spectrum of our understanding of hair growth, the clear concepts behind the pathogenesis, diagnostic procedures, and current treatment options, and to stimulate the reader to delve even deeper into the challenging task of diagnosing and helping their patients with hair problems.

We are extremely proud of, and grateful to, the world's leading experts for their excellent contribution to this textbook. The quality and diversity of topics presented are testament to the devotion of everyone involved in this project.

We would like to thank Dr. Kathrin Hillmann, who was key in assembling and preparing this book. In addition, we would like to thank the Berlin team represented by Hannelore Thomas for helping us to realize the dream of a dedicated textbook that reflects the state of the art in the "World of Hair".

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Chapter 1

Biology of the Hair Follicle

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1.1 Introduction

Over the last few decades, progress in molecular biology and genetics, as well as the development of new experimental approaches, has brought together scientists from all fields. Developmental biologists, geneticists, endocrinologists, and dermatologists now study the many diverse facets of hair follicle biology including neuroectodermal–mesenchymal interactions, immunology, pigmentation, and stem cell biology.

In humans, the main function of the hair shaft is its role as an important facet of appearance. Across cultures for centuries, the decoration and styling of scalp hair has been a means of social communication and display of social identity or status. Hair is so important in our society that hair loss, as well as the overgrowth of terminal hair on the body or face, has deleterious effects on self-esteem.

The clinical relevance of hair and hair growth impairment goes far beyond the diagnosis and treatment of hair disorders, as the following examples illustrate. More than 300 genetic conditions have hair abnormalities as a component feature, and so the evaluation of hair growth is an easy, first-level diagnostic tool in pediatric dermatology and genetics. Identifying hair abnormalities can also be a useful aid in the diagnosis of suspected defects and diseases in their early stages, before more severe symptoms of progressive multi-organ involvement develop. As hair is continuously shed and allows for non-invasive collection, it can also be an important component of evidence in forensic medicine. Finally, drugs, chemicals, and biological substances accumulate and are stored in hair fiber where they can be detected and measured.

1.2 History

In the fourth century BC the philosopher Aristotle suggested that hair formed from sooty vapors exhaled through the body's pores that hardened on contact with air. These vapors were residues that the body was unable to dispose of through concoction, the process whereby food was made into nourishment (blood) for the body.

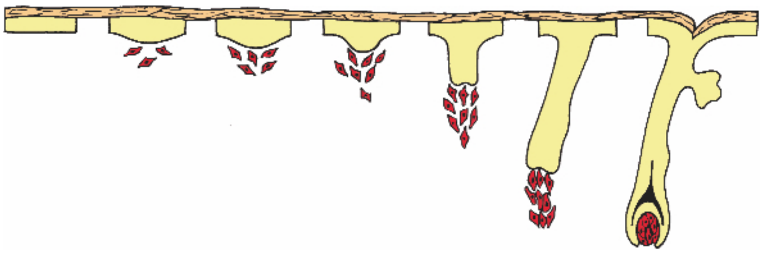


Fig. 1.1. Morphogenesis of the human hair follicle. Hair follicle formation is the result of complex sequential signaling events between the dermal mesenchyme and the overlying epithelium. Morphologically, induction, organogenesis, and cytodifferentiation phases can be determined

In the eleventh century AD, Saint and scientist Albertus Magnus, unable to determine a special role for the hair, assigned it an excretory function, and believed that scalp hair fiber was the product of gross humor and phlegm divested from the brain. Early in the sixteenth century, a microscopic study of mouse hair fiber allowed scientist William Derham to see medullae and led him to suggest the hair fibers were tubules for the evacuation of humor and perspiration from the body [18]. With the development of histological tissue analysis it became clear that hair fiber was rooted deep in the skin "implanted in the pyramidal papillae," through which the hairs were thought to imbibe nourishment from the adjacent humors [10]. Only with the careful study of the skin and hair follicles by anatomists in the nineteenth century were hair follicle structure and its embryogenesis fully defined, and the mechanism of hair fiber growth correctly extrapolated [88].

Recent advances in molecular biology and genetics have revolutionized our understanding of hair cycling and hair growth. In particular, an increasing number of spontaneous or experimentally generated murine mutations have provided valuable insights into the functional significance of selected gene products in hair follicle morphogenesis and cycling. The identification of animal models of human diseases has helped to evaluate the relevance of candidate gene approaches.

1.3 Hair Follicle Morphogenesis

Hair follicle appendage formation involves a complex sequence of signals between the dermal mesenchyme and the overlying epithelium. The precise initiating stimulus is still to be defined. Morphologically, induction, organogenesis and cytodifferentiation phases can be determined, and a division of hair follicle formation events into eight distinct developmental stages in rodents and humans can be made [75]. The development of human hair follicles first starts between the 8th and 12th weeks of gestation. Probably in response to dermal signaling elements, which are expressed in gradients over the developing fetus, thickening of the primitive epithelium forms placodes that induce the aggregation of underlying dermal cells to mesenchymal condensates [19] – the first visible stage in hair follicle development (Fig. 1.1). The very first hair follicle placodes are seen in the eyebrow, upper lip, and chin regions. Placode formation subsequently expands in a wave caudally and ventrally over the skin of the fetus. The dermal condensates issue instructions to the cells of their associated overlying ectodermal placodes to proliferate and initiate penetration of the dermis; stage 2 of development. As the epithelial cells grow downwards into the dermis, the dermal condensate cells lead the way. The hair follicles grow into the dermis at an angle to the skin surface, with the degree of angle determined by the location of the hair follicle [66]. The initial placode formation stage gives way to an early peg stage (stage 3) hair follicle. By 12–14 weeks' gestation, the epithelial base of the hair pegs on the scalp invaginates to envelop the dermal cell condensates and form dermal papillae. This stage of development is described as the bulbous hair peg stage, or stage 4 in development [28].

In stage 5 at 13–16 weeks' gestation, the superficial portions of the hair follicles subsequently develop two distinct, asymmetrical bulges of cells on the "posterior" side of the follicle, which is at an obtuse angle to the skin surface. The upper bulge closest to the skin surface eventually forms the sebaceous gland, while the lower bulge forms the location of the presumptive follicular stem cells and will later anchor the developing arrector pili muscle to the hair follicle. The arrector pili muscle itself develops independently of the hair follicle and is usually first seen in the dermis near the developing sebaceous gland [66]. The arrector pili muscle grows downwards to connect with the bulge region as the follicle pushes deeper into the dermis. Notably, the arrector pili muscle does not develop in hair follicles growing perpendicular to the skin, such as eyelash hair follicles, follicles of the external auditory canal, and those of the nasal orifice. The outer cells of the bulge, destined to become the sebaceous gland, proliferate and some differentiate into lipogenic cells that progressively accumulate lipid. Maternal hormones cause sebaceous gland hypertrophy and temporarily increase the synthesis and secretion of sebum during the second and third trimesters. With release under the influence of maternal hormones at birth, the sebaceous glands become relatively quies-

cent until endogenous hormone production increases in puberty. In humans, some hair follicles will develop a third superficial bulge of cells above the cells destined to become the sebaceous gland. The development of this third bulge of cells indicates the formation of an apocrine gland [30]. In humans the face and scalp are the most common locations for hair-follicle-associated apocrine gland development. While hair-follicle-associated formation of apocrine glands can be common in other mammalian species, in humans the association is relatively infrequent.

In the second trimester, the hair follicles differentiate to eventually form the seven layers of cells in concentric cylinders seen in mature hair follicles. Beginning near the bulb at the end of stage 4 or at the beginning of stage 5, a core of epithelial cells separates from the peripheral epithelial cells which later become the outer root sheath, continuous with the non-follicular epithelium. The epithelial cell core, resting on the top of the dermal papilla, further differentiates into the inner root sheath Henle, Huxley, and cuticle layers, and the central core of matrix cells that proliferate and give rise to the hair fiber cuticle, cortex and, later in terminal hairs, the medulla [9, 18]. Stage 6 is defined by the visible development and growth of the hair fiber. As the hair fiber and its inner root sheath elongate, the peripheral epithelial cells move aside to allow the cone of the central core of cells to move upwards away from the bulb. By 19–21 weeks' gestation, the developing hair follicles reach stage 7, in which the hair canals form. In stage 8 the hair follicles are fully formed and the first hair fibers erupt from the skin. The initial lanugo hair of the first anagen hair growth phase grows until 24–28 weeks of gestation.

1.4 Molecular Mediation of Hair Follicle Morphogenesis

These developmental events of hair follicle morphogenesis are controlled by a complex network of sequential activation and inactivation of autocrine, paracrine, and endocrine signaling pathways. Recent research has identified multiple regulatory factors and the essential nature of their influence on hair follicle development, but these molecular controls are not well understood [47]. How these regulators interact with each other, their relative significance, the degree of redundancy in the signaling system, and how these signals determine the development of such a complex structure, its size, and subsequent growth cycle characteristics are still largely unknown.

The source of the initial signal for hair follicle development remains unproven. Currently, evidence suggests the first signal emanates from the embryonic mesoderm, but whether the epithelium plays a purely passive role in the induction of the first signal is not known. The earliest known molecular pathway activated during hair follicle development involves β-catenin, an intracellular mediator of gene expression. Research has shown that β-catenin is essential for keratinocyte stem cell fate decision [89]. Over-expression of stabilized β-catenin in the epidermis of transgenic mice has been shown to induce de-novo hair follicle morphogenesis, demonstrating its fundamental importance in hair follicle development [24]. In contrast, a lack of functional β-catenin results in keratinocyte differentiation to an epidermal role and a failure of hair follicle development.

Products of the WNT gene family are secreted glycoproteins that regulate cell proliferation, migration, and specification of cell fate in the embryo and adult [27]. WNT proteins are classified in part according to their ability to promote stabilization and prevent degradation of β-catenin in the cell cytoplasm. The β-catenin-dependent WNT pathway signals through cytoplasmic stabilization and accumulation of β-catenin. As it accumulates, it translocates to the cell nucleus where it forms complexes with members of the lymphoid enhancer-binding factor/T cell factor (LEF/TCF) family of DNA-binding factors to activate gene transcription. In mice, activation of WNT signaling is required in the skin for the successful induction of hair follicle development [69]. At this stage in our understanding of hair follicle embryogenesis, WNT-gene-coded proteins are the first extracellular mediators known to be involved in hair follicle development. However, it is possible that there is an even earlier gene-coded signaling mechanism that activates hair follicle development and promotes WNT gene signaling.

With the initiation of the first signaling and placode formation, a plethora of extracellular and intracellular mediators is expressed. WNT signals transduced by β-catenin and LEF-1 can elicit the expression of ectodysplasin A (EDA). Experimentally, expression of EDA, activation of its receptor (EDAR), or subsequent downstream activation of the NF-κB pathway mediated by EDAR will each lead to hair follicle development [15]. Not surprisingly, expression of LEF-1 will also induce hair follicle formation as will expression of Noggin, transforming growth factor β2 (TGFβ2), TGFβR-II, β1 integrin and neural cell adhesion molecule (NCAM). Fibroblast growth factors FGF1, FGF2, FGF4, and receptor FGFr2 may also have a hair follicle inductive role, based on studies with chick embryos and the promotion of feather formation. In contrast, multiple inhibitors of hair follicle placode formation, including BMP-2, BMP-4, p75NTR and activin βa, are also expressed in embryonic skin. To add to the already crowded signaling schema, genes encoding several secreted molecules capable of inhibiting the inhibitors of hair follicle in-

duction, including Follistatin, and Gremlin, are also expressed in developing follicles. The apparently very complex interplay between activators and inhibitors of hair follicle formation, and the respective regulators of activator and inhibitor product expression likely determine the distribution of follicles in the skin [81].

With the development of hair follicles underway, yet more factors are required to regulate the hair germ in its growth and differentiation. Platelet-derived growth factor A (PDGFA) and Sonic hedgehog (Shh) are secreted by the ectodermal cells of the developing hair follicle. They are required for the condensation of the presumptive dermal papilla cells and for progression of the follicle placode to the peg/bulge hair stages. Asymmetric expression of Shh also polarizes the hair, ensuring outgrowth of the hair follicle in a defined direction. While activin βa can act as a placode inhibitor, activin βa in combination with Shh, hepatocyte growth factor (HGF) and its receptor (MET), transcription factor SOX18, and TGFα have been identified as driving factors during organogenesis. These and other products impel the downgrowth of the hair germ into the dermis. In stages 5–8 of hair follicle morphogenesis, the follicle differentiates into the complex structures that make up a mature hair

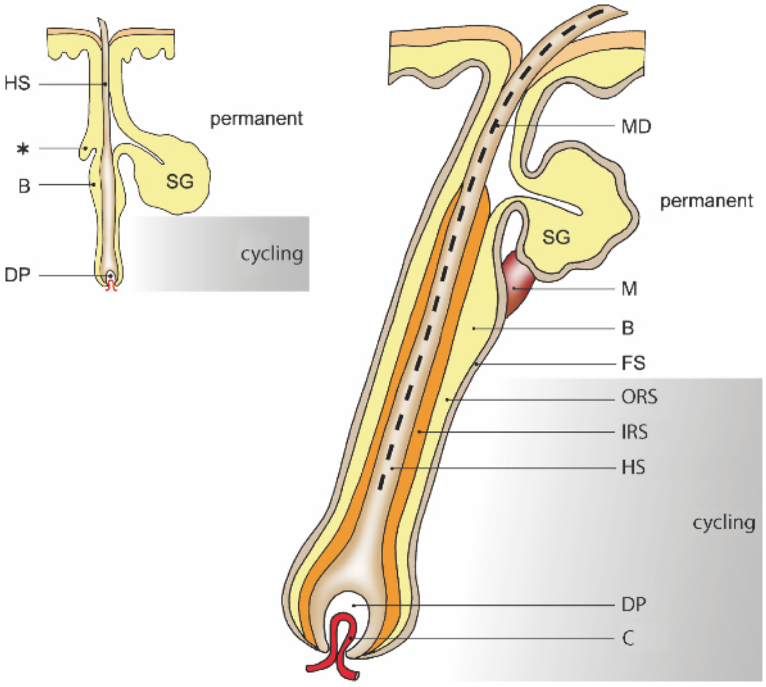


Fig. 1.2 Anatomy of the pilosebaceous unit. All hair follicles follow a common architecture. Together with the sebaceous gland (*SG*) and the arrector pili muscle (*M*), the hair follicle is part of the so-called pilosebaceous unit. The fibrous sheath (*FS*) and the epithelial outer and inner root sheaths (*ORS, IRS*) form concentric layers, which ensheath the hair shaft (*HS*). Hair growth results from the proliferative activity of matrix keratinocytes in the bulb, which sit on the dermal papilla (*DP*). The dermal papilla is a condensate of specialized mesenchymal cells with important inductive properties. It also provides nutrition via a capillary loop (*C*), which is especially prominent in terminal hair follicles. The permanent, superficial component has to be differentiated from the transient cycling component of the hair follicle, which includes the bulb. The morphological dividing line between these two components lies below the bulge (*B*) region and the insertion of the arrector pili muscle (*M*). The size and shape of the hair follicles, however, vary with body location and potential functions. In anagen phase, for example, vellus hair follicles from the retroauricular region (*left*) are approximately six times shorter than scalp hair terminal follicles (*right*). Each hair follicle has characteristic features. Vellus hair shafts, in contrast to terminal hair shafts, are usually devoid of a medulla (*MD*). Skirt-like epithelial structures (*), however, can only be found in vellus hair follicles

follicle. Yet more signaling pathways and product expression are involved in this process, including Notch1, keratinocyte growth factor (KGF), nude, bone morphogenic protein 2 (BMP2), BMP4, MOVO1, multiple HOX genes and, again, mediators such as WNT gene products and their transcriptional activators such as LEF-1. The precise interactions between all these signaling events, however, remain to be unraveled [81].

1.5 Anatomy of the Mature Pilosebaceous Unit

The hair follicle is a complex mini-organ of its own. Each hair follicle is formed by multiple mesenchymal and epithelial cell layers, in total comprising more than 20 different cell populations. Together with the sebaceous gland and the arrector pili muscle, the hair follicle is part of the so-called pilosebaceous unit. The proportions of these components vary among the different hair follicle types (Fig. 1.2).

The general hair follicle structure can be divided into regions based on morphology, on whether the structure derives from the ectoderm or mesoderm, and on hair cycling characteristics. At its most basic, divisions can be made between the permanent, superficial structure and the transient cycling component of the hair follicle, which includes the hair bulb (Fig. 1.3). The morphological dividing line between these two components lies just below the bulge region and insertion of the arrector pili muscle [48]. The permanent portion of the hair fol-

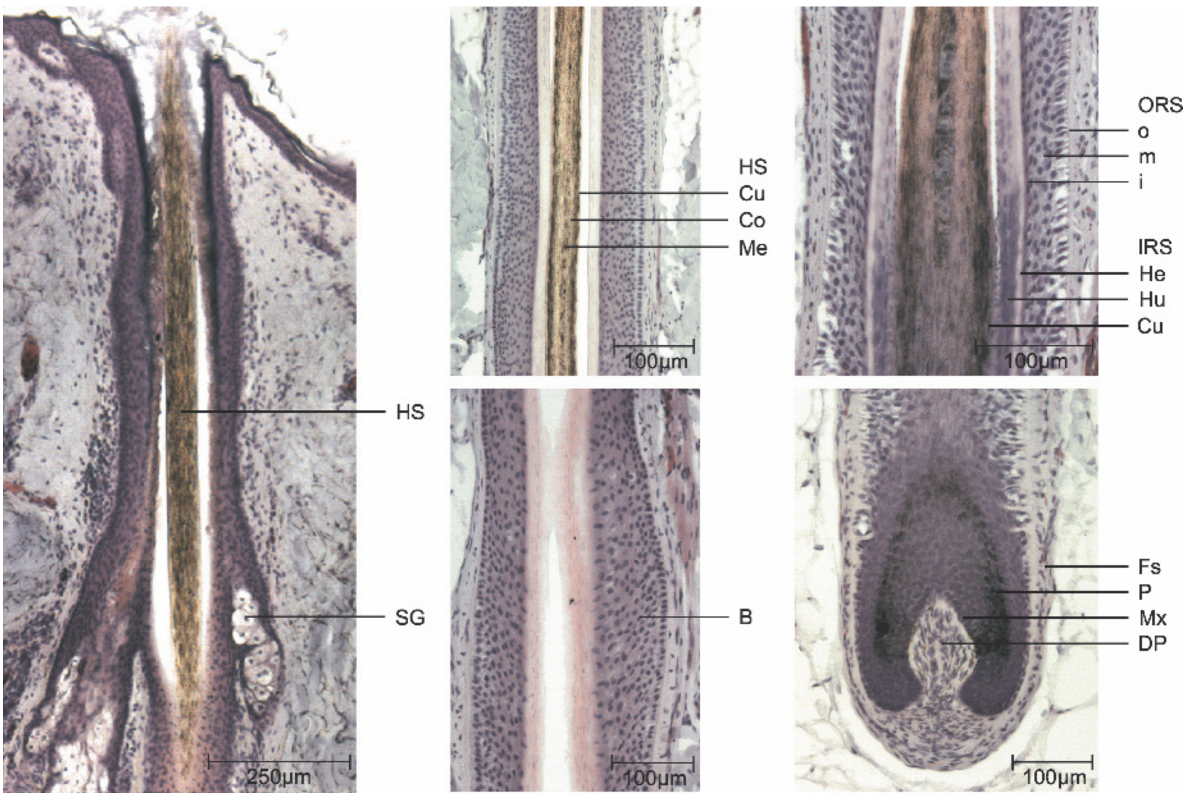


Fig. 1.3 Histomorphology of a human anagen-stage terminal hair follicle. The hair follicle itself is a complex mini-organ formed by multiple concentric mesenchymal and epithelial cell layers. The fibrous sheath (*Fs*) ensheathes the outer root sheath (*ORS*) with an outer (*o*), middle (*m*), and inner (*i*) region and the inner root sheath (IRS), which is further subdivided into Henle layer (*He*), Huxley layer (*Hu*), and cuticle (*Cu*). Matrix cells (*Mx*) in the hair bulb overly the dermal papilla (*DP*) and give rise to the hair shaft (*HS*), which consists of the cuticle (*Cu*), the cortex (*Co*) and, only in terminal hair follicles, the medulla (*Me*). Melanocytes in the bulb transfer pigment (*P*) to the hair-forming keratinocytes. The bulge region (*B*) represents a specialized compartment of the outer root sheath close to the insertion site of the arrector pili muscle, which forms a niche for epithelial and neuroectodermal stem cells as well as various immature cell populations including immature Langerhans cells and mast cells

licle structure can be further subdivided. From the skin surface to the point of the sebaceous gland duct opening to the hair canal it is called the infundibulum. The superficial part of the hair follicle infundibulum, the acro-infundibulum, is lined by intact epidermis including a well developed stratum corneum and a stratum granulosum. Continuous loss of epidermal differentiation occurs towards the isthmus of the lower part of the infundibulum, the infrainfundibulum.

The part between the sebaceous gland duct opening and the bulge is called the isthmus. The isthmus is a border zone relatively devoid of distinctive features though notably the thick vitreous membrane between ectoderm and mesoderm visible elsewhere in anagen-stage hair follicles becomes much thinner here. The hair follicle isthmus wall consists of two or three rows of flattened cells, whose angle of orientation can be observed to change along the length of the isthmus as the outer root sheath merges with the skin epithelium. The bulge region below the isthmus, which provides the insertion site of the arrector pili muscle, also harbors the so-called bulge region, a specialized compartment of the outer root sheath which forms a niche for epithelial and neuroectodermal stem cells as well as various immature cell populations including immature Langerhans cells and mast cells (see Sect. 1.10.1). The permanent portion of the hair follicle, the part that extends from the skin surface down to lower end of the bulge region, does not undergo significant cyclic changes. However, the presence of hair follicles, their size, and their density effectively lead to a considerable enlargement of the skin surface, which is of particular interest with regard to percutaneous penetration processes.

The inferior unit, which extends from the bulge to the base of the hair follicle bulb, can be further subdivided into the bulb and suprabulbar region. The epithelial compartments of the hair follicle include the outer root sheath and the inner root sheath, both composed of different cell sublayers, and the matrix cells (see Chap. 7). The outer root sheath extends from the matrix cells in the hair bulb up to the entry level of the sebaceous duct. Outer root sheath cells contain clear vacuolated cytoplasm filled with large amounts of glycogen. Below the isthmus, the outer root sheath is not keratinized. However, at the level of the isthmus, where the inner root sheath disintegrates, the outer root sheath keratinizes without forming granules. Outer root sheath cells express a large diversity of mediators, hormones, and receptors. The inner root sheath consists of three layers, the Henle, Huxley, and cuticle, all of which keratinize. It hardens before the presumptive hair fiber does and is, hence, thought to control the cross-sectional and longitudinal shape of the hair produced (Fig. 1.4). The mesenchymal sheath is separated from the epithelial root sheaths by a vitreous or basal membrane. This whole complex is surrounded by a dense vascular network. Free nerve endings form a cuff and provide the basis for intensive piloneural interactions [49].

Hair growth results from the proliferative activity of matrix keratinocytes, which give rise to the hair shaft and the inner root sheath. They are localized in the bulb where they sit on the dermal papilla, the condensate of specialized mesenchymal cells with important inductive properties. In fact, surgical removal of the dermal papilla and the lower dermal sheath prevents hair growth, which indicates the importance of these specialized mesenchymal cells as the key signaling center in hair follicles. Nutrition of the papilla and the overlying matrix cells is provided via a capillary loop located within the dermal papilla of terminal hair follicles. Vellus hair follicle dermal papillae typically do not contain capillaries.

1.6 Hair Fiber Properties

The hair fiber, the most visible product of the hair follicle, is formed of keratin proteins, which are organized as a two-phase intracellular composite consisting of the keratin fibers embedded in an amorphous matrix. Recent genome analyses have increased the number of identified human keratins to 54, grouped into acidic type I and basic-to-neutral type II intermediate filaments (11 of the 28 type I keratins and 6 of the 26 type II keratins are hair keratins). The complex expression patterns of type I and type II hair keratins in the hair follicles as well as hair-specific expression of epithelial keratins are summarized in Table 1.1 [77]. To accommodate the growing number of keratin genes, a new consensus nomenclature for mammalian keratins was recently proposed, which also allows the incorporation of keratins from other mammalian species [76]. The matrix proteins, also referred to as keratin-associated proteins, are a major component of the hair fiber and play a crucial role in forming a strong hair shaft through a cross-linked network with keratin intermediate filaments. Generally, division occurs into high-sulfur proteins, ultra-high sulfur proteins and high-glycine-tyrosine proteins, which are differentially expressed in the cortex, cuticle, and matrix [58]. In terms of raw elements, on average, hair is composed of 50% carbon, 20% oxygen, 17% nitrogen, 6% hydrogen, and 5% sulfur. Hair also contains trace amounts of magnesium, arsenic, iron, chromium, and other metals and minerals.

The visible hair shaft of terminal hair follicles consists of three layers: cortex, cuticle, and medulla. The central medulla contains polygonal cells with a sponge-

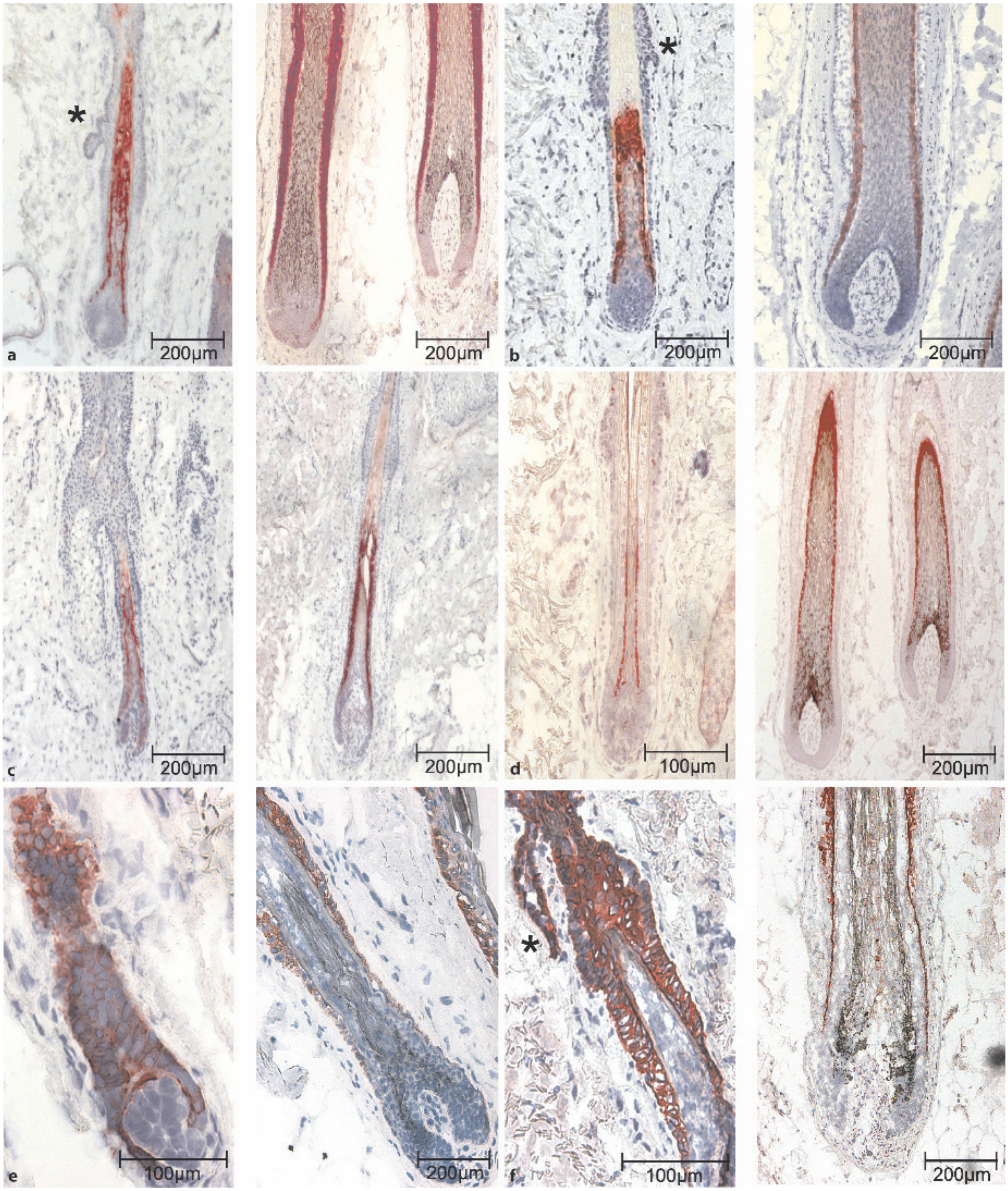


Fig. 1.4a–f Cytokeratin expression pattern in human vellus and terminal hair follicles. The expression of differentiation markers such as cytokeratins is closely related to the anatomical layers of the hair follicle. Except for some hair-follicle type-specific characteristics, such as the skirt-like epithelial structure of vellus hair follicles (*), all hair follicles follow the same architecture. This is illustrated in this figure which, in each *panel* (**a**–**f**) displays one vellus hair follicles (*left*) and one terminal or intermediate hair follicle (*right*), respectively. The inner root sheath displays immunoreactivity against cytokeratin 13 (**a**) and trichohyalin (**b**), while immunoreactivity against cytokeratin 18 can predominantly be found in the Huxley layer (**c**). Anticytokeratin 7 specifically stains the cuticle (**d**). Cytokeratin 17 (**e**) and cytokeratin 19 (**f**) are markers of the outer root sheath

Table 1.1 Human hair keratins and hair-follicle-specific epithelial keratins with their expression sites[a] [77]

Type I	Expression site	Type II	Expression site
Hair keratins (hair fiber keratins)			
K31 [Ha1]	Entire cortex	K81 [Hb1]	Mid cortex
K32 [Ha2]	Cuticle	K82 [Hb2]	Cuticle
K33a [Ha3-I]	Mid cortex	K83 [Hb3]	Mid cortex
K33b [Ha3-II]	Mid cortex	K84 [Hb4]	Absent from the hair follicle present in tongue
K34 [Ha4]	Upper cortex	K85 [Hb5]	Matrix, precortex cuticle
K35 [Ha5]	Matrix/precortex, cuticle	K86 [Hb6]	Mid-cortex
K36 [Ha6]	Mid cortex		
K37 [Ha7]	Central cortex vellus hairs; medulla sexual hairs		
K38 [Ha8]	Single cortex cells		
K39 [Ka35]	Upper cuticle		
K40 [Ka36]	Cortex, medulla, upper cuticle		
Hair-follicle-specific epithelial keratins			
K25 [K25irs1]	IRS (Henle, Huxley, cuticle), medulla	K71 [K6irs1]	IRS (Henle. Huxley, cuticle), medulla
K26 [K25irs2]	IRS (Upper cuticle)	K72 [K6irs2]	IRS (cuticle)
K27 [K25irs3]	IRS (Henle, Huxley, cuticle), medulla	K73 [K6irs3]	IRS (cuticle)
K28 [K25irs4]	IRS (Henle, Huxley, cuticle), medulla	K74 [K6irs4]	IRS (Huxley)
		K75 [K6hf]	Companion layer, medulla

[a]The keratin designations follow the new keratin nomenclature [76] with their former names in *brackets*.

like appearance. In terminal hair produced in childhood the medulla may be absent or fragmented. In fine vellus hair fiber the medulla is always absent. Around the medulla, the cortex forms a layer of cornified fibrous cells with a longitudinal orientation. When fully developed, these cells are packed with keratin filaments. The hair fiber cortex contains melanosomes, which determine the color of the hair fiber. Homogenous oval eumelanin granules and lamellar pheomelanin granules, in variable composition and density, form the wide spectrum of dark to fair hair. The outermost layer of the hair fiber, the cuticle, consists of multiple layers of corneocytes. It is thin and translucent allowing light to penetrate to the cortex pigments.

There are a wide range of biometric measurements of hair, such as the diameter and structure of the hair shaft, most of which are genetically programmed (see Chap. 24). Terminal hair diameter and cross-sectional shape are key differentiating features, which can be approximated by hair color and ethnicity. While Caucasians typically have terminal scalp hair with a cross-sectional diameter ranging from as low as 40 μm in blonde-haired people to 90 μm in dark-haired individuals, average hair fiber diameters are higher overall in African and Asian populations (Table 1.2). Hair cross-sectional shape also varies with ethnicity. While Caucasians typically grow hair with an elliptical cross-sectional shape consistent with straight or wavy hair, Asian hair is typically circular in cross-section consistent with straight hair [72]. In contrast, African populations have a very elliptical or even ribbon-like cross-sectional shape to their terminal hair fiber. The ribbon-like shape makes hair relatively

Table 1.2 Terminal hair diameter [16, 17, 72]

Type	Diameter – typical range (µm)
Blonde-haired Caucasian	40–80
Dark-brown/black-haired Caucasian	50–90
Red-haired Caucasian	50–90
African (African-American)	60–100
Asian (far East)	80–120

inflexible across the long cross-sectional axis but very flexible across the short axis consistent with curly hair. The shape of the hair shaft is partly formed by the shape of the hair follicle. Major determinants of the overall individual appearance of the hair fibers are the position of the hair bulb relative to the rest of the hair follicle, the size and shape of the dermal papilla, and the curvature of the hair follicle along its length. These parameters determine the diameter and cross-sectional shape of the hair shaft and the number of twists and windings (curl) per unit length of each individual hair. While in large part these properties are defined by the hair follicle that produces the hair fiber, environmental factors from chemical exposure to friction may also modify the nature of the hair fiber.

Hair fibers are enormously durable material with the potential to survive thousands of years, as seen with Egyptian mummies for example. Hair is also very strong: the cross-sectional area of hair fiber and the structural integrity of the cortex determine its overall strength. Healthy hair fiber has a tensile strength around 180–190 MPa [90], which makes hair about as strong as copper wire of the same diameter. Hair fiber also has elastic properties: extension of 10% of its original length under tensile stress is possible without damage. Extension of 35%–50% is possible, but results in permanent damage of the inner fiber structure. Hair shaft abnormalities that may reduce hair strength and quality are due to genetic changes in the shape, diameter, and structural composition, to surface cuticle defects, or are due to environmental manipulation such as physical or chemical damage to the cuticle and cortex. In curly hair, the cuticle of the outer curl is relatively thin and more fragile and consequently is sensitive to exogenous stress such as heat or chemicals. Disruption and loss of the hair cuticle, whether through genetic defects or acquired from the environment, significantly weakens the overall strength of the hair and may result in splitting and breakage. More limited changes in the structure of the cuticle can lead to impaired water retention in the underlying cortex with loss of humidity. For a healthy appearance, hair fibers ideally need to retain approximately 17% humidity. In fact, water retention up to 35% is possible. Hair length also varies up to 2% depending on the air humidity [45, 90].

1.7 Hair Follicle Types

Hair and hair follicles occur diversely all over the human body except on palms of the hands, soles of the feet, glabrous foreskin, and lip vermillion. Based on the structure and shape of the hair fiber, gross size, and time of appearance on the body, several hair follicle types can be differentiated (Table 1.3). Generally, lanugo hair-producing hair follicles, vellus hair follicles, intermediate hair follicles and terminal-hair-producing follicles can be identified [71]. A hair follicle may move from one category to another as it changes size and hair fiber production over time.

1.7.1 Lanugo Hair

Lanugo hair is fine, soft, poorly pigmented and has no central medulla. Produced in utero, it is the first hair growth produced by developing hair follicles. Lanugo hair may also be observed in adults with various forms of hypertrichoses [82].

1.7.2 Vellus Hair

Vellus hair is non-medullated, fine, and poorly pigmented. Vellus hair continues to grow throughout life. Even in areas usually considered to have only terminal hairs, such as the scalp, vellus hair may constitute 7%–25% of the hair present.

Table 1.3 Typical hair characteristics

Hair type	Characteristics
Lanugo	<30 µm diameter; >2 mm length
Vellus	<30 µm diameter; <2 mm length
Intermediate	>30 µm diameter; <60 µm diameter; > 2 mm length
Terminal	>60 µm diameter; >2 mm length

1.7.3 Intermediate Hair

Intermediate hair is first observed postnatally as the scalp hair growth subsequent to the initial lanugo hair growth. Intermediate hair is characterized by a relatively rough cuticle, sparse pigmentation and a fragmented or absent medulla.

1.7.4 Terminal Hair

Terminal hair has a larger cross-section diameter as compared to other hair fiber types. It is pigmented, with the exception of those hairs affected by canities, and grows for a significant length.

The size and shape of terminal hair varies with body location and potential function. Terminal scalp hair serves a key role as protection from UV light and as an insulator against heat and cold. Specialized terminal hair such as eyebrows and eyelashes may protect the eyes by draining or sweeping away fluids and dust [50]. Eyelashes have the largest diameter of all body hair, strong pigmentation, and they have a relatively short active growth phase. Nasal hair may play a role in preventing insects and other airborne material from entering the nasal cavity (Table 1.4).

This classification of hair follicles, based on the nature of the hair fiber produced, can be further refined by the morphological characteristics of the hair follicles themselves. The primary anatomical distinction of human hair follicles depends largely on gross size to differentiate those producing vellus hair from those producing terminal hair. Vellus hair follicles are small and penetrate the reticular dermis but not the subcutaneous fat layer. As a morphological characteristic, vellus hair follicles frequently display skirt-like epithelial structures or perifollicular connective tissue capsules, with a striking clear space between the outer root sheath and these skirt-like structures, or between the outer root sheath and the perifollicular connective tissue capsule. This space is filled with mucinous substance that is rich in perifollicular nerve endings and, among other cell types, contains elongated fibroblasts and mast cells [56]. The typical dermal papilla in a vellus hair follicle contains just 10–30 cells. Compared to vellus hair follicles, a typical terminal scalp hair follicle dermal papilla contains 200–400 cells and correspondingly the rest of a terminal hair follicle is much larger. Terminal hair follicles reach into the deep dermis and their bulbs are located in the subcutaneous fat.

Further subclassification can be made based on the morphology of hair follicles. For example, sebaceous hair follicles in seborrheic regions of the skin display relatively large well-developed sebaceous glands associated with small, fragile hair follicles. Hair follicle types may also be differentiated by their functional characteristics, such as the different responsiveness to androgens of terminal hair follicles in the scalp as compared to those in the beard, the axilla, and the pubic region. While all hair follicles have the same basic developmental and structural characteristics, there is significant variation in morphological presentation. However, of the hair follicles located in the different body regions, hair follicles of one predominating subtype form rather homogenous groups with only moderate intra- and inter-individual variability.

1.8 Hair Cycling

Traditionally, three phases of the growth cycle are recognized: a growth phase (anagen phase I–VI), a regression phase (catagen), and a resting phase (telogen). For

Table 1.4 Types of terminal hair in humans [23]

Hair type	Length – typical range (mm)	Description
Scalp	100–1000	Medullated with tapered tip in uncut hair
Eyebrow and eyelash	5–10	Medullated and curved with punctuate tip
Beard and moustache	50–300	Complex medullary processes, more irregular in structure, blunt tip
Body	5–60	Irregularly medullated, fine tip
Pubic	10–60	Coarse, kinked, irregular and asymmetrical cross-section
Axillary	10–50	Coarse, less kinked than pubic hair, blunt tip, often abraded due to friction

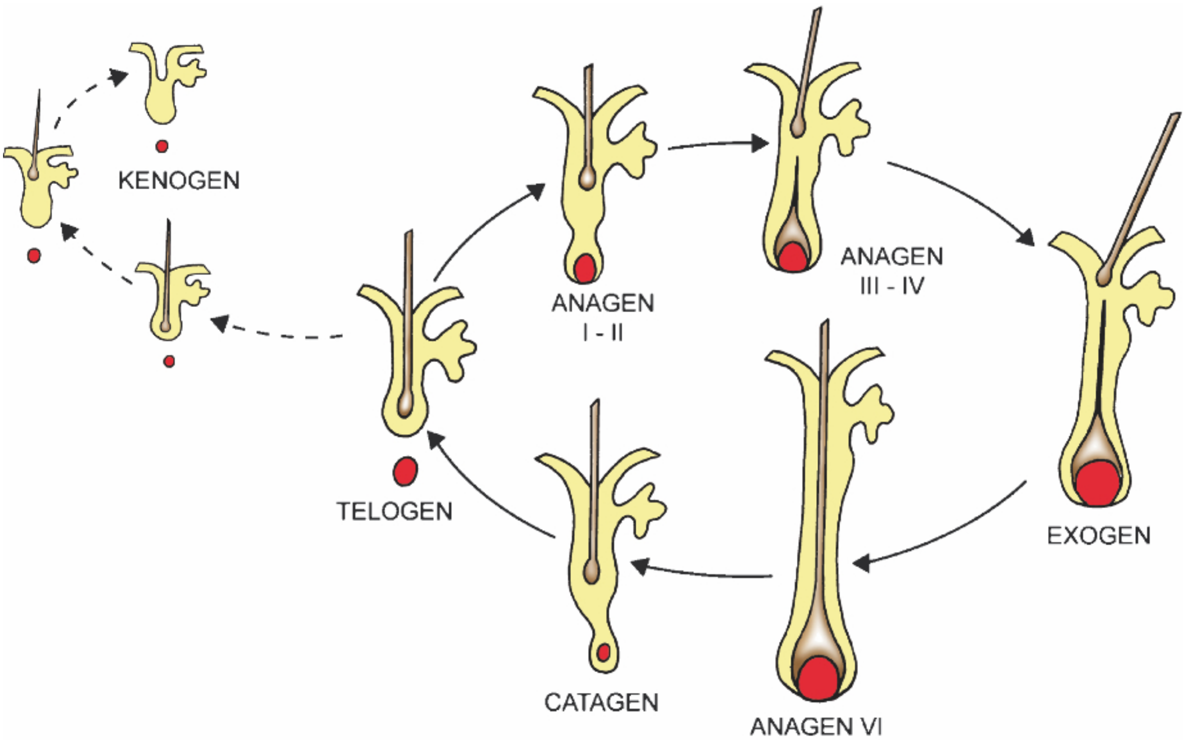


Fig. 1.5 Hair cycle. During one hair cycle a complete remodeling of the non-permanent portion of the hair follicle occurs, which is controlled by finely tuned changes in the local signaling milieu. Traditionally, three phases of hair growth are recognized: a growth phase (*anagen I-III*), regression phase (*catagen*), and resting phase (*telogen*). Recent research suggests that shedding of the hair fiber is an active process, which has led to the introduction of the term "exogen" to describe this event. As another novel phenomenon in hair cycling, empty hair follicles after shedding of the hair fiber were reported. This interval of the hair cycle, in which the hair follicle remains empty after the telogen hair has been extruded and before a new anagen hair emerges, has been named "kenogen"

identifying and classifying each of the individual stages of hair follicle cycling (Fig. 1.5) refer to [53]. These cyclic transformations are controlled by finely tuned changes in the local signaling milieu, based on changes in the expression of cytokines, hormones, neurotransmitters and their receptors as well as transcription factors and enzymes, which act via endocrine, paracrine or autocrine routes. In fact, hair cycling parallels morphogenesis involving multiple signaling events incorporating developmental pathways such as reoccur during the different hair cycle stages. The hair cycle includes a complex remodeling and regeneration of the complete non-permanent portion of the hair follicle. It is not just the hair follicle epithelium, but also the mesenchyme, the extracellular matrix, the vasculature and innervation, and the hair-follicle-associated cell populations that undergo dramatic changes. In fact, in species with synchronized hair follicle cycling, the architecture and physiology of the entire skin, including its immune and gene expression status, undergo substantial changes subsequent to prior switches of multiple hair follicles from one stage of their cycling activity to another.

1.8.1 Anagen

During the anagen phase, the hair is actively growing and materials are deposited in the hair shaft by cells found in the follicle. Metabolically active and dividing cells above and around the dermal papilla of the follicle grow upward during this phase to form the hair shaft. The anagen phase includes not only the growth of the hair, but also a highly increased proliferative rate of all hair follicle cells in all epithelial compartments, with the highest activity observed in matrix cells. Anagen duration is genetically predetermined and varies with the

size and body location of the hair follicle. An anagen growth phase may last several years, as seen in terminal hair follicles on the scalp, but anagen may persist for just a few weeks in terminal hair follicles on the extremities (for associated melanin production and hair shaft pigmentation see Chap. 4).

1.8.2 Catagen

The anagen phase is followed by a short resting phase, catagen, which can be divided into eight subphases starting with late anagen and ending in early telogen. The regression of the hair follicle in catagen is characterized by a cessation of protein and pigment production, involution of the hair follicle, and a fundamental restructuring of the extracellular matrix. Massive apoptosis in the infrabulbar, transient, portion of the hair follicle leads to regression of the hair follicle and the formation of a fibrous streamer. Because the onset of these apoptotic events seems to be predetermined and finely orchestrated, programmed cell death is probably the more accurate term to describe these events. When the part of the hair follicle in contact with the lower portion of the hair becomes attached to the hair shaft, the so-called club hair is formed. Catagen is the first component of the initial hair cycle occurring after morphogenesis.

1.8.3 Telogen

In telogen, the hair follicle has regressed to about half of its previous size and does not extend beyond the upper dermis. Morphologically, a "finger" of epithelial cells overlies a cluster of dermal fibroblasts; the remains of the dermal papilla. The dermal papilla is no longer enveloped by surrounding epithelial cells and sits as a small ball of cells in close association with the epithelial cell finger. The epithelial cells of the lower telogen follicle do not show significant DNA or RNA synthesis, nor is there any synthesis of proteins characteristic of the anagen follicle, such as trichohyalin and the hair cortical keratins. Notably however, keratin 14 (K14) synthesis does continue in the epithelial sac to which the telogen hair fiber anchors. In telogen follicles the volume of the dermal papilla extracellular matrix is much reduced, and dermal papilla cells have scant cytoplasm and are relatively quiescent. The telogen hair shaft, the club hair, can be retained for months in this epithelial sac.

1.8.4 Exogen

Recent research suggests that shedding of the hair fiber is a highly controlled, active process, which differs from the quiescence normally found during the telogen phase. Consequently, the term "exogen" has been introduced to describe this event as a specific process of its own during hair follicle cycling [80]. In fact, more detailed studies on this process suggest that the former concept, based on the assumption that the newly formed hair fiber pushes the resting shaft outward to effect shedding, is unlikely. When a shed hair shaft root is compared to a plucked telogen hair shaft root by light or electron microscopy, major morphological differences are apparent. The telogen root is made of packed nucleated cells which show intracytoplasmic fractures surrounding a cornified core making up the shaft. The exogen root, in contrast, is made of very few cells and these cells are separated at their outer edge by intercellular cleavage. The morphology of the hair root suggests that the exogen process involves a proteolytic event that occurs between the moving cells of the telogen shaft base. The nature of this shedding process remains to be identified. A possible role of desmoglein and proteolytic events was suggested [37].

1.8.5 Kenogen

As a novel phenomenon in hair cycling, empty hair follicles after shedding of the hair fiber were reported when using phototrichograms and the term "kenogen" was suggested to describe this interval of the hair cycle in which the hair follicle remains empty after the telogen hair has been extruded and before a new anagen hair emerges. Kenogen can be reproducibly observed in healthy skin; however, frequency and duration have been reported to be greater in men and women with androgenetic alopecia [68].

1.8.6 Duration of the Hair Cycle

The duration of the different phases depends on the type and localization of the hair follicle. Under physiological conditions, 85% of the scalp hair is in anagen and approximately 15% is in the telogen phase [71, 87]. The anagen phase of scalp hair follicles typically persists for 2–6 years, although a few individuals may have anagen growth phases of much longer duration. The duration of anagen is a major determinant of the maximal hair length. The anagen phase of hair follicles of the eyebrows, in contrast to scalp hair follicles, is only 70 days, while eyelashes grow for 100–150 days. The duration of telogen in hair follicles is also an important consideration when understanding the consequences of changes in the hair growth cycle. The body hair follicles are characterized by an increased telogen frequency and duration as compared to scalp hair follicles (Table 1.5). Un-

Table 1.5 Hair cycle duration with body location [14, 35, 36, 62, 85]

Location	Hair growth state	Typical time duration
Scalp	Anagen	2–6 years
	Catagen	2–3 weeks
	Telogen	3 months
Beard	Anagen	4–14 weeks
	Telogen	10–18 weeks
Arms	Anagen	6–12 weeks
	Telogen	7–13 weeks
Legs	Anagen	19–26 weeks
	Telogen	13–34 weeks

der physiological conditions, each hair follicle continues to cycle throughout life.

1.8.7 Hair Growth and Cycle Regulation Potential of the Dermal Papilla

The potent inductive ability of dermal papilla cells to promote hair follicle formation has long been recognized. The size and secretory power of the dermal papilla determine the size of the anagen bulb, and subsequently the diameter of the hair shaft produced by the hair bulb, and the rate of hair growth, respectively [20]. The dermal papilla also dictates the duration of anagen and thus, in combination with the rate of hair growth, the potential maximum length that hair fiber can reach. What determines the duration of anagen within dermal papilla cells is not clear, but several hypotheses have been suggested involving variations on a biochemical clock mechanism [59]. Different concepts, which are still being controversially discussed, include the idea of accumulation of an endogenous inhibitor during anagen, which, at a threshold level, inhibits mitosis thereby causing transition to catagen phase. Dictation of hair cycling length by the (limited) number of mitoses of slow-cycling epithelial cells in response to mesenchymal signals is being discussed, as is the presence of as yet unidentified endogenous oscillating signals or embryonic pathmakers.

Whilst it is unlikely that the epithelial component is entirely passive in determining the size and shape of hair follicles, numerous studies have confirmed that the mesenchymal signaling component predominates. Many investigators have found that follicular dermal papilla cells dissected from the base of an anagen hair follicle, either fresh or after tissue culture expansion, can induce new hair follicle formation in rodents if placed in proximity to non-follicular epithelium [34]. This process has been variously called the follicular neogenesis model, hair follicle replication, and hair multiplication. In addition, labeled cultured dermal papilla cells and cells from the bulbar connective tissue sheath of rodent vibrissae have been shown to be incorporated into resident pelage hair follicles making them larger and prolonging the duration of anagen, suggesting that the introduced cells can override the inherent properties of resident dermal papilla cells [43]. This process has been called the morphogenetic switch model, follicular amplification, or, in the case of damaged follicles, follicular reactivation. Thus far only one published study has indicated that follicular replication is possible in humans. Reynolds et al. transplanted microdissected connective tissue sheath from the scalp of a man to the forearm of a woman. After 3–5 weeks, new follicles were observed at the site of transplantation with the mesenchymal portion arising from the transplanted donor cells [70]. These and other studies demonstrate that dermal papilla cells retain knowledge of the size and shape of the hair follicle they should form and they retain a memory of their hair cycle clock.

1.8.8 Developmental Pathways, Cytokines, Growth Factors, and Neuroendocrine Factors

Especially in the anagen phase, parallels are seen in the development of the newly formed hair follicles compared to the events observed during morphogenesis. In fact, part of morphogenesis is recapitulated in each hair cycle, involving the expression of morphogens and mediators concerned with pattern formation, including the Hedgehog and Wingless family. Shh and its downstream targets, which drive proliferation during folliculogenesis, also promote cell proliferation in anagen hair follicles. Wnt signaling determines the differentiation of epithelial stem cells into hair follicle keratinocytes. Ablation of Wnt signaling blocks initiation of a new hair cycle. Moreover, activation of the Wnt pathway has been reported to be necessary to maintain the cultured papilla cells' ability to induce hair follicles. Epimorphin, a mesenchymal morphogen that has been shown to mediate epithelial–mesenchymal signaling interactions in various organs, is involved in telogen-to-anagen transition. Differential gene expression analyses in the skin recently identified genes encoding hair-specific keratins and keratin-associated proteins (KAPs) as major groups of presumptive downstream effectors of the homeobox gene Hoxc 13. The natural hair cycle, however, involves many more signaling events and pathways (including

cytokines, growth factors, adhesion molecules, neuroendocrine mediators, and hormones), and the equipment of each cell with specific subsets and combinations of receptors and enzymes regulates the responses to these numerous, frequently redundant, stimuli [2].

Although sensitive to changes in the systemic blood levels of hormones, the fine-tuning of synthesis, receptor expression and receptor binding, and enzyme activity in and around the hair follicle are major determinants of normal hair cycling This is especially so since the hair follicle has been shown to produce complete hormone cascades on its own, which act on the different cell populations in endocrine, paracrine, and autocrine ways. For example, the production and expression of signals and receptor components of the gonadotrophin-releasing hormone (GnRH), corticotrophin-releasing hormone (CRH), and pro-opiomelanocortin (POMC) systems have been characterized in detail leading to the term "brain–hair follicle axis" with suggested equivalence to the hypothalamo–hypophyseal axis in the brain (see Chap. 3).

The differential expression of receptors and enzymes also provides the basis for the variable responsiveness to sexual hormones and their metabolites in the different hair follicle types. Androgens have diverse effects on hair follicles in different body regions. Androgen-related effects vary from essentially non-existent (e.g., on eyelashes), to weak (on temporal and suboccipital region hair), to moderate (on extremity hair), to strong (on facial, parietal region, pubic, chest, and axillary hair). Differential effects are also observed in scalp hair; occipital terminal hair follicles, for example, are largely independent of androgen action, while androgen-dependent beard hair in males forms only under adequate androgen stimulus. Also, in males, hair loss in androgenetic alopecia is most pronounced in the tempoparietal regions above the temples and on the vertex. Androgen sensitivity of the individual hair follicles also remains after transplantation of pilosebaceous units; a feature called "donor dominance" (see Chap. 22).

1.9 Hair Growth Changes with Age

The first hair to be produced by the fetal hair follicles is lanugo hair, which is usually shed between the 32nd and 36th weeks of gestation. In up to one-third of babies, however, lanugo hair growth, to some extent, is retained until birth. The presence of lanugo hair over the entire body at delivery can be a sign of prematurity.

During the fetal period, all scalp hair follicles are in the same hair cycle phase. Within a few weeks after birth, regression of the hair follicles to catagen occurs in two waves starting at the frontal zone, which then migrates over the scalp from the forehead to the nape of the neck. There is an area over the occiput in which the primary hairs do not enter telogen until after birth. These hairs remain in the scalp for 8–12 weeks and then fall. As telogen hairs predominate on the occiput, their fall commonly produces an area of temporary, localized alopecia. In the subsequent hair cycle, intermediate hair fibers form the first scalp hair and an asynchronous hair cycle is established following a mosaic pattern. There is considerable variation in the age at which the mosaic pattern is fully developed. Frequently, children have only sparse hair growth in their initial months of life until the first postnatal telogen phase. Subsequent hair growth is much stronger and more consistent in density. On the scalp, the fully developed terminal hair follicle is detectable around 12–16 months of age.

After the loss of the fine lanugo hair, vellus hair follicles cover most of our body surface and, hence, are the most prominent hair follicle type in the postnatal period. Initially, only the hair of the eyebrows, eyelashes, and scalp develops into terminal hair and becomes highly pigmented. Over time, depending on the age of the individual, gender, and body region, vellus hair follicles can transform and begin to produce terminal hair fiber. At puberty, the vellus hair in some body areas is replaced by longer, coarser, pigmented terminal hair. Growth first starts in the pubic region; then the eyelashes and eyebrows become thicker as compared to prepuberty. Axillary hair and male facial hair begin to appear about 2 years after the growth of pubic hair begins. Body and beard hair continues to grow long after puberty, stimulated by male hormones that, paradoxically, also cause regression of scalp terminal hair follicles into vellus hair-like follicles in androgenetic alopecia. The likelihood of the presence of androgen-induced terminal hair growth on body regions varies with age, sex, and ethnicity. In general, Caucasians have a greater frequency of body hair growth as compared to Asian and African peoples. While beard hair growth is almost always present in Caucasians, beard growth can be more limited in Asian ethnic groups and extremely limited in aboriginal peoples.

Postpuberty hair-growth rates vary with body location (Table 1.6). Prepuberty, hair growth is most rapid on the vertex of the scalp, but postpuberty the hair-growth rate on the vertex slows and becomes less rapid as compared to the hair-growth rate on the occiput in both males and females. The rate of terminal hair growth on the scalp occiput, thigh, and eyebrow remains relatively consistent throughout adult life, but the growth rate of more androgen-responsive hair follicles on the chin and axillary hair changes with advancing age. Hair follicles on the chin in men are the fastest growing hair follicles,

Table 1.6 Rate of terminal hair growth in adults [54, 63, 74]

Location	Typical hair growth per day (mm)
Chin	0.38
Scalp	0.35
Axilla	0.30
Thigh	0.20
Eyebrow	0.16

Table 1.7 Typical numbers of scalp hair follicles [22, 41]

Type	Number
Blonde-haired Caucasian	130,000
Dark-brown/black-haired Caucasian	110,000
Red-haired Caucasian	90,000
African (African-American)	90,000
Asian (far East)	90,000

Table 1.8 Hair follicle density with age (absence of alopecias) [6, 19, 25, 83]

Location	Mean density of hair follicles in skin (/cm^2)
Full-term fetal scalp	1135
Adult scalp	615
Full-term fetal forehead	1060
Adult forehead	765
Full-term fetal thigh	480
Adult thigh	55

Table 1.9 Estimated number of hair follicles in the skin by body region [83]

Location	Number of follicles
Head	1,000,000
Trunk	425,000
Arms	220,000
Legs	370,000
Approximate total	2,000,000

producing 0.38 mm of fiber per day in adulthood, but this rate slows somewhat with age [54]. Androgens may also be a factor in the reduction of the hair-growth rate and atrophy of axillary hair follicles in old age.

At birth, each human being possesses between two million [83] and five million [21] vellus and terminal hair follicles. Of this total, 100,000–150,000 hair follicles are located on the scalp [21, 50]. The number of scalp hair follicles varies with the individual's skin, hair color, and ethnicity. Dark-haired individuals tend to have fewer scalp hair follicles than fair-haired individuals (Table 1.7). Overall, scalp hair density is slightly greater in boys than in girls and all individuals have a density gradient of hair follicles from the vertex to the occiput.

Hair follicle density on the body changes in different body regions with age (Table 1.8). All hair follicles form during embryonic development and no additional follicles are naturally formed after birth in humans [7]. This is not always true for other mammals as, for example, deer antler velvet involves annual formation of new hair follicles [42]. As compared to an adult, the surface area of skin in newborn humans is relatively small and so the hair follicles are relatively densely packed together. With growth, the same number of hair follicles must be spread over a progressively larger unit area of skin. Different regions of the body grow at different rates and, subsequently, hair follicles in some regions are spread further apart than in others. While our heads grow somewhat after birth, the greatest increase in growth occurs in our limbs. Consequently, hair follicle density on the head remains relatively high while density on the lower arms and legs is much reduced in adults (Table 1.9).

1.10 Specialized Hair Follicle Compartments

1.10.1 Stem Cells

The cyclic activity of the hair follicle requires the regeneration and new assembly of its non-permanent portion during each new hair cycle. This enormous plasticity is accomplished by the presence of multipotent adult stem cells, which reside in rather undifferentiated, quiescent states and form precursors, transient amplifying cells, which provide further proliferation and differentiation into the different cell types. Such pools of adult stem cells have been identified in various self-regenerating tissues [12]. Label-retaining cell analyses, which followed BrDu or [^{3}H]TdR labeling for periods of up to over 1 year, revealed that the slowest cycling cells within

the skin reside in a specialized compartment of the hair follicle epithelium termed the bulge region. Here, cell label retention of 14 months was observed in mice and of at least 4 months in humans [13]. The bulge region is a contiguous part of the outer root sheath, which marks the lower end of the permanent portion of hair follicles. On histological sections of human hair follicles, it can be readily identified as a unilateral thickening of the outer root sheath. The quiescent nature of bulge cells was also demonstrated by labeling experiments in mouse models and on human skin grafted to immunodeficient mice, where uptake of the labeling substances [^{3}H]TdR and BrDu was only observed at the onset of the anagen phase [31]. Studies using colony-forming experiments as well as holoclone analyses confirmed a high proliferative potential [52]. While earlier studies suggested that bulge-derived cells also migrate into the interfollicular epidermis, recent investigations using transgenic mouse models demonstrated that such migration only occurs under wound healing conditions, while the homeostatic regeneration of the interfollicular epidermis emanates from the interfollicular epidermis itself [32, 40]. This supports the clinical observations and early studies on animal models suggesting that hair follicles significantly contribute to epidermal repair [4].

To understand why stem cells are preferentially located in a specific niche such as the bulge region, studies on the microenvironment in the bulge are gaining importance. Balanced c-myc expression seems to be crucial, as its overexpression in transgenic mice causes follicle stem cells to proliferate and to terminally differentiate [5]. Microarray profiling has identified over 150 genes, which are preferentially expressed in the bulge region relative to interfollicular epidermis. Purification and enrichment of bulge stem cells, however, remains a challenge, especially since critical differences in gene expression have been found between human and murine bulge cells. Due to their relative quiescence, bulge cells are more susceptible to the accumulation of genetic damage and retention of carcinogens over prolonged periods of time [51] and consequently they may be more likely to form tumors. For example, there is molecular evidence for their involvement in the formation of basal cell carcinomas and trichoepitheliomas [1]. The identification of melanocyte stem cells [57], mesenchymal stem cells [39], mast cell precursors [38], immature Langerhans cells [26], and neural-like stem cells [3] further underlines the enormous plasticity of hair follicle cells and intensive research efforts are ongoing to explore ways to utilize the hair follicle as an autologous source for stem cell recovery for the treatment of a wide variety of diseases.

1.10.2 Immunology

The hair follicle, as a physiological break in the skin barrier, is a conduit for intensive interactions with the environment. Accordingly, antigen-presenting cells can be found at particularly high densities in hair-follicle-bearing skin [84]. They are particularly concentrated around the upper portion of the hair follicles, where they are found not only in the suprabasal layer, but also in the basal layer of the outer root sheath. In contrast, however, very low numbers of immune cells are found in the transitory hair follicle compartments [11]. The restricted distribution of intraepithelial T cells and Langerhans cells, accompanied by suppressed major-histocompatibility-complex-II- (MHC-II-) dependent antigen presentation, the virtual absence of MHC class I expression, and the concomitant high expression of immunosuppressive mediators such as alpha melanocyte-stimulating hormone (α-MSH), transforming growth factor β1 (TGFβ1), and adrenocorticotropin (ACTH), suggest that the hair follicle, between the bulb and the lower bulge region, constitutes an area of transient immune privilege. Just like other immunoprivileged tissues, such as the anterior eye chamber, the hair bulb is devoid of lymphatics and is ensheathed by a special extracellular matrix barrier, both of which might hinder immune cell trafficking.

The immunoprivileged state occurs in a hair-cycle-dependent manner. In mouse skin, local production of TGFβ1, ACTH and αMSH is highest when all hair follicles are synchronized in the anagen phase [78]. In fact, human hair follicles are MHC-I-positive during telogen and the late anagen phase [33]. The physiological significance of the immune privilege in the anagen hair growth phase, however, remains poorly understood. It is conceivable that its breakdown plays a role in the pathogenesis of autoimmune diseases affecting the hair follicle such as alopecia areata, lupus erythematosus, scleroderma, graft-versus-host-disease or lichen planopilaris. The inflammatory reaction in alopecia areata targets predominantly the transitory compartments of anagen hair follicles, an observation which gave rise to the concept of immune-privilege collapse in alopecia areata pathogenesis [60]. This hypothesis of functional immunoprotection against autoimmune reactions is supported by recent research by Rosenblum et al. suggesting that CD200, which reportedly inhibits autoimmunity, is an important regulator of the immune-privileged state of the human hair follicle and that skin deficient in CD200 is highly susceptible to hair-follicle-associated inflammation and immune-mediated alopecia [73]. Extensive further studies, however, will be required to unravel all the different facets of the hair follicle immune system

and their implication in the pathophysiological events observed in inflammatory hair diseases.

1.10.3 Neuroimmunological and Neuroendocrine Interactions

The hair follicle is both a target for, and a source of, immunomodulatory stress mediators [61]. The dense perifollicular meshwork of sensory nerve endings is closely associated with mast cells, endothelial cells, and macrophages [64], rendering the hair follicle a potential site for intensive pilo-neural interactions. Neuroendocrine mediators including substance P, cortisol, ACTH, CRH, POMC, and neurotrophins, all of which are expressed in the hair follicle, exert hair-growth-modulating effects. Local regulatory feedback systems similar to the hypothalamic–pituitary–adrenal axis have been identified (see Chap. 3). In particular, vellus hair follicles on the head, upper trunk, and upper extremities are innervated by Merkel nerve endings, i.e., specialized Merkel cells filled with neuroendocrine granules, which occur in association with nerve fibers [86] (see Chap. 5).

1.10.4 Melanocytes

Melanocytes, which transfer melanosomes to the surrounding keratinocytes and thereby direct the pigmentation of the hair fiber, lie in the matrix zone. Melanocyte activity is hair cycle dependent. At the end of each hair cycle melanocytes reduce melanin production and retract their dendrites. Therefore, localized canities can often be found as an unpigmented proximal end to a telogen hair fiber, which is unpigmented because melanin production stops at the end of each hair cycle slightly in advance of hair fiber growth termination. In aged grey and white hair, the melanocyte number in the basal hair matrix is reduced, remaining melanocytes display signs of degeneration, and the hair fiber only contains melanin debris [79] (see Chap. 4). Neuroectodermal crest stem cells, which may give rise to immature melanocytes, have been identified in the bulge region.

1.11 Experimental Techniques

Due to the complex structure and regulation of the hair follicle, with more than 20 cell populations and numerous signaling events involved, experimental hair research is a challenging task and the experimental model has to be chosen carefully and appropriately for each question to be answered. Being localized at the skin surface, hair growth and hair abnormalities are, on first glance, easy to monitor. Hair fibers and hair roots are easily accessible for non-invasive collection. In clinical diagnostics, traditional trichograms allow evaluation of hair cycling anomalies using simple light microscopy. Phototrichograms, and the recent development of the TrichoScan™ technique allow quantification of hair growth in vivo [29]. In addition, the use of global photography techniques is a popular approach in treatment evaluation. Whilst these approaches are very useful for disease diagnosis and clinical treatment trials, they provide relatively limited information about the hair follicle in the skin. To characterize hair follicles requires more invasive techniques. In the clinic this generally involves tissue biopsy and histological analysis of the hair follicle structure. For the research laboratory, many more experimental techniques have been developed as aids to our understanding of skin appendage formation and growth.

There are advantages and limitations to any experimental technique. Conventional analysis methods of sections of cryo-preserved or paraffin-embedded tissue remain invaluable screening tools for the evaluation and validation of expression patterns of RNA or protein, using techniques such as in situ hybridization and immunohistochemistry respectively. Material for gene expression profiling can also be harvested from plucked hair follicles. In fact, RNA of sufficient quantity and quality to use for microarray hybridizations can be obtained from as little as one single hair fiber. However, while these approaches using tissues enable evaluative studies to be performed, they do not permit studies to determine the functional significance of a particular gene or its product in hair growth or disease. For functional studies, one must use living tissue in some fashion.

Animal models of hair follicle development and hair diseases have grown in popularity in recent decades. Developmental biology using model organisms such as *Drosophila*, *Xenopus* and zebrafish have provided valuable insights into the role of conserved signaling pathways including *Hedgehog* or *Wingless* in pattern formation and the formation of skin appendages in general. Mammalian models, especially the development of genetically engineered mice which can be used to study the regulatory events of hair follicle development and hair growth, are directly relevant to hair follicle biology in humans [67]. Rodent models in particular have many advantages that enable research. Their ready availability, rapid breeding, known genetics in inbred strains, the ability to modify their genetic profile, the ability to control environmental input, and the ability to conduct invasive procedures are all advantages in the use of animal

models. Rodent models are broadly categorized into two types: those with spontaneous hair follicle abnormalities or disease, and those where genetic manipulation has been conducted to produce transgenic (gene overexpression) or knockout (gene inactivation) mice for a specific gene of interest [55].

Rodent models may be further classified based on the nature of the trait features they present. Rodent models available for hair biology and hair disorder research include those with: (1) a failure in hair follicle formation and consequently abnormally low numbers of hair follicles; (2) disorders of hair morphogenesis where hair follicles form but fail to fully develop; (3) hair follicle cycling disorders where hair follicles form and develop but fail to cycle correctly; (4) hair follicle structure and/or sebaceous gland structure disorders often leading to hair shaft defects and alopecias; (5) disorders of hair fiber pigmentation; (6) immunological abnormalities resulting in alopecias; (7) neuroendocrine abnormalities; and (8) models of environmentally mediated diseases where exogenous factors are introduced to modify hair growth [44]. While there are perhaps a few hundred spontaneous murine hair-disorder models, since the introduction of transgenic technology literally thousands of genetically modified mice have been generated, many of which are probably relevant to understanding hair biology and disease.

Most regulatory events in hair follicle growth are conserved between rodents and humans. However, some critical differences have been described at the molecular level and animal models of hair disorders may not fully reflect the morphological presentation of disease in humans. Consequently, especially when it comes to the pathogenesis of human diseases, it is essential to carry out studies on human hair follicles in addition to animal model studies. There are of course numerous ethical limitations to experimental research directly on human volunteers. Typically, there are limited numbers of individuals willing to take part in research, their genetics are often unknown, their environment cannot be regulated, and invasive approaches are limited. However, as understanding human hair disorders is often the ultimate goal in hair research, studies with human volunteers are important. Where procedures cannot be conducted directly with humans, techniques have been developed to utilize human tissues.

Transplant models, where diseased hair-bearing human skin is transplanted onto immunodeficient mice, provide a great opportunity to study and manipulate human hair growth. Skin transplantation to rodents has been used in research on androgenetic alopecia where no satisfactory rodent model is available, alopecia areata, and for the study of several forms of genetic trichoses. Immunodeficient mice have been extensively used as hosts for tissue transplants or cell implantation to aid our understanding of basic hair biology. Such an approach, using tissue hosts, has significant advantages, particularly in the evaluation of drugs and their impact on hair growth. However, the approach also has some disadvantages. By isolating human tissue by grafting to a mouse host, the tissue is being removed from any systemic effects from elsewhere in the body; this is particularly relevant in inflammatory diseases. Plus, while biochemical signals in mice are often cross-reactive with human cell receptors this is not always the case. Consequently, a mouse host environment is somewhat different from a human hair follicle's in situ environ.

Culture techniques are a further option for functional research. Hair follicles contain readily identified cell populations of interacting cells that are clustered in discrete sites. Cell types can be isolated and continue to show pronounced interactive abilities when cultured in vitro. Primary cell cultures from murine and human hair follicles, including hair follicle keratinocytes, dermal papilla cells and melanocytes, provide important information on the expression of mediators and the behavior of single cell populations [8, 46]. They are, however, of more limited value, because they often lose their organ-specific characteristics within a few passages. As the knowledge on hair growth and its regulation becomes more and more complex, more sophisticated in vitro models are required which allow the investigation of the complex interactions during normal hair growth and in response to bioactive compounds. In this context, the whole-organ culture model first developed and described by Michael Philpott is a valuable tool [65].

Research conducted using animal models, "human models," in vitro models, or perhaps in the future computer models, can each provide significant information. However, each approach has its limitations and rarely does just one model provide the complete picture. To fully understand hair biology and hair disease involves collating and assimilating information for all its diverse sources to piece together what is a very complex picture of hair biology.

1.12 Clinical Relevance

Before hair disorders can be studied, it is necessary to define the normal state of hair biology and hair growth. Without knowledge of what is a "normal" state one cannot characterize what is regarded as "abnormal." The many evaluative studies on hair follicles, from the highly detailed studies of histologists over 150 years ago to the advanced genetic analysis of today, have revealed many secrets of normal hair follicle development, growth, and cycling. We now have a solid understanding of the es-

sential principles of hair biology, though there is much more to learn.

Major advances in our understanding of hair biology have helped to identify key pathogenetic events in common hair diseases including the altered androgen response and subsequent hair follicle miniaturization in androgenetic alopecia, or perifollicular inflammation involvement in alopecia areata and lichen planopilaris. Further, due to the complex interplay of signaling events in hair growth and cycling, hair follicles are extremely sensitive to endogenous influences, such as hormonal imbalances, systemic diseases, or nutritional defects. Environmental factors may also affect hair follicle growth, such as in response to stress or pathogens, or the impairment of mitotic activity caused by drugs resulting in changes in hair shaft caliber and breakage of hair fibers. Excessive or continuous exposure to toxins may induce massive impairment of hair growth leading to a loss of dystrophic anagen hair fibers.

Information on hair biology, hair formation, and cycling is directly relevant to understanding the pathogenesis of clinically apparent hair disorders and the course of disease, not only for the trichologist but also for the patient. Communication of such information to the patient, apart from meeting the patient's need for education on their disease, tremendously helps to improve compliance during treatment. For example, because of the hair growth kinetics, topical minoxidil treatment in androgenetic alopecia frequently requires regular application over the course of several months before a recovery of hair growth can be evaluated.

1.13 Outlook – Future Developments

Advances in molecular biology and gene expression profiling have led to a significant increase of knowledge about the genes and signaling pathways involved in hair growth and hair cycling. New insights into the complex regulation of hair follicles have led to a more finely defined understanding of the pathogenesis of diseases such as alopecia areata and androgenetic alopecia. Because current therapeutic concepts are still rather unspecific in their action, current research concentrates on the development of more focused strategies that will allow specific, targeted treatment of the various manifestations. Subgrouping of patients, by gene expression profiling for example, in the future may help to determine the most effective therapeutic option for each individual patient.

The growing knowledge of the various signaling pathways involved in hair growth may further lead to the identification of new drug targets, opening the door for the development of novel drugs as, for example, with the development of biologicals for the treatment of psoriasis. The development of novel drug delivery systems that allow better penetration of active compounds into the hair follicles, and possibly targeting of specific compartments within the hair follicles, may allow an increase in the efficacy of established treatments and of new therapies with a reduction of side-effects. Last but not least, advances in stem cell isolation and purification may enable us to bioengineer hair follicles to provide efficient hair replacement therapy in cases where conventional treatments fail.

Summary for the Clinician

Hair and hair follicles occur in a wide diversity all over the body except on the palms, soles, glabrous foreskin, and lip vermillion. Lanugo hair-producing hair follicles, vellus hair follicles, intermediate hair follicles, and terminal hair follicles can be identified. The hair follicle is a complex mini-organ in its own right. Each hair follicle is formed by multiple mesenchymal and epithelial cell layers, together comprising more than 20 different cell populations. Together with the sebaceous gland and the arrector pili muscle, the hair follicle is part of the so-called pilosebaceous unit. Relevant anatomical divisions can be made between the permanent, superficial structure and the transient cycling component of the hair follicle, which includes the hair bulb. The morphological dividing line between these two components lies below the bulge region, the putative site of epithelial stem cells and precursor populations of melanocytes, mast cells and Langerhans cells. Hair growth results from the proliferative matrix of keratinocytes that reside in the bulb, where they sit on the dermal papilla, a condensate of specialized mesenchymal cells with important inductive properties. Hair cycling is traditionally divided into a growth phase (anagen I–VI), a regression phase (catagen), and a resting phase (telogen). The shedding of the hair fiber has recently been identified as an active process of its own (exogen). The events of hair follicle morphogenesis and cycling are controlled by a complex network of sequential activation and inactivation of autocrine, paracrine, and endocrine signaling pathways. The hair follicle is surrounded by a dense meshwork of blood vessels and nerve endings. Multiple specialized cell populations can be found associated with the different compartments of the hair follicle, including melanocytes, neuroendocrine cells and immune cells.

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Chapter 2

The Endocrine Control of the Hair Follicle

2

Valerie A. Randall

Synonyms

hormone metabolism, hormonal control, endocrine metabolism of the hair follicle

Key Features

- Hair follicles can produce different types of hair (length, thickness, colour) at various times in an individual's life due to the follicle's capacity to regenerate a new hair during the hair cycle. This allows hairs to change to correlate with alterations in season or sexual development, etc.
- The type of hair produced is under endocrine control with androgens being key regulators of human hair growth; several other hormones are involved, particularly in other mammals, including melatonin, prolactin, melanocyte-stimulating hormone (MSH) and oestrogens.
- Androgens have paradoxically different effects on human hair follicles depending on their body site. This ranges from stimulation, e.g. on the face, axilla, pubis and chest, through no effect on the eyelashes, to inhibition on parts of the scalp, causing balding in genetically susceptible individuals.
- All androgen effects require an intracellular androgen receptor in the hair follicle cells and most, except for pubic and axillary follicles, also require the intracellular enzyme 5α-reductase type 2 to metabolize testosterone to its more potent metabolite 5α- dihydrotestosterone.
- Exactly how androgens regulate hair follicles is not fully established, but most aspects appear to be coordinated via the mesenchyme-derived dermal papilla situated at the base of the follicle. In the current hypothesis androgens from the blood bind to androgen receptors in dermal papilla cells, altering their gene expression, particularly of paracrine signalling molecules, which influence the activity of the other follicular cells. Key signals identified so far include insulin-like growth factor-1 (IGF-1) in growth stimulation and transforming growth factor-β (TGF-β) in inhibition.
- Androgen-dependent hair disorders are not easily controlled. Currently, antiandrogens, such as cyproterone acetate or spironolactone, can be used for hirsutism in women and 5α-reductase type 2 inhibitors, such as finasteride, for androgenetic alopecia. The most common non-endocrine treatment for hair loss is minoxidil, a vasoactive drug. Further understanding of the mechanism of androgen action in hair follicles should lead to the development of better treatments.

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2.1 Introduction

The hair follicle, a highly unusual dynamic organ found only in mammals, is fascinating from many viewpoints. It is an essential mammalian characteristic important for warm bloodedness and for mammalian evolutionary success, and has an almost unique ability in mammals to regenerate itself, recapitulating many steps of embryogenesis as it does so [29] (see Chap. 1). In addition, in human beings it is a paradoxical tissue where the same hormones, the androgens, can cause stimulation of hair growth in many areas, e.g. beard, whilst simultaneously inhibiting hair follicles on the scalp causing balding [46, 50, 52].

Correctly functioning follicles are crucial to the survival of many mammals – loss of fur or faulty colouration may rapidly lead to death from cold or predation. Although hair loss is not life threatening for human beings, hair is very important for most people. Many Western men spend significant time every day shaving their beards, while hairdressers are everywhere and large amounts are spent on hair care. This reflects the very important roles hair plays in human communication, both in social and sexual contexts, and explains why hair growth disorders such as hirsutism, excessive male pattern hair growth in women, and hair loss {such as alopecia areata, an autoimmune disease affecting both sexes at all ages [49] (see Chap. 15)} cause serious psychological distress. Androgenetic alopecia or male pattern hair loss [51] (see Chap. 9) even causes negative effects among men who have never sought medical help.

Hormones co-ordinate changes in the type of hair produced, usually in parallel with changes in the individual's age and stage of development or alterations in the environment such as day length [9]. Hormones instruct the follicle to undergo appropriate co-ordinated changes so that during the next hair cycle the new hair produced differs in colour or size from that present originally. In human beings the key hormones are the androgens [46, 50, 52]. When androgens increase at puberty the development of more hair in the axilla and pubis in both sexes or on the face in men is welcomed as a sign of sexual maturity. However, if androgens stimulate hirsutism in women, or initiate androgenetic alopecia on the scalp, then the clinician's aid is requested. Currently, available treatments for hair disorders, particularly androgen-dependent hirsutism and androgenetic alopecia, are rather limited and have widespread effects on the body. Greater understanding of how androgens alter the type of hair produced by the hair follicles should facilitate the development of more effective and selective treatments. This chapter will review the functions of hair, outline how the hair follicle growth cycle allows hairs to be changed and summarize the endocrine control of seasonal changes and pregnancy before focusing on how androgens act, predominantly on human hair follicles. Hormonal control of pigmentation will be covered in Chap. 4.

2.2 History

The importance of the testes for the development of normal hair growth was recorded by Aristotle 300 years B.C., well before the concept of hormones, i.e. soluble chemical messengers in the blood, was developed in the 1800s. In the mid 1900s an American anatomist, James Hamilton, clarified much of our current knowledge of androgens and human hair growth by comparing hair growth from childhood to old age in normal men and women from different genetic backgrounds and castrated men [17]. More recently the importance of the regulatory mesenchyme-derived dermal papilla at the base of the follicle in determining the type of hair produced [60] has led to the concept that hormones, particularly androgens, alter hair growth by acting via the dermal papilla to enable co-ordinated changes in the hair follicle [46, 50, 52].

2.3 Structure and Function of Hair Follicles

2.3.1 Function

Mammalian skin produces hair everywhere except for the glabrous skin of the lips, palms and soles; human hair growth is less obvious in humans than in other mammals, with tiny, virtually colourless *vellus* hairs in many areas. Outside the skin hairs are thin, flexible tubes of dead, fully keratinized epithelial cells which are very variable in colour, length, diameter and cross-sectional shape; inside they form part of living hair follicles, cylindrical epithelial downgrowths into the dermis which enlarge into hair bulbs surrounding a mesenchyme-derived dermal papilla at the base (see Figs. 2.1, 2.2).

In many mammals hair is important for insulation, an appropriate colour for camouflage and as a protective physical barrier, e.g. for ultraviolet light. Hair follicles are also sometimes specialized as neuroreceptors, e.g. whiskers, or for sexual communication, e.g. the lion's mane. In contrast, the main functions of human hair are protection and communication, although seasonal variation in human hair growth [7, 42, 53] and hair erection (goosebumps) in response to cold remain (reviewed [52]). The hairs seen in childhood are mainly protective: the eyebrows and eyelashes stop foreign bodies entering the eyes and scalp hair probably prevents sunlight, cold and physical damage to the head and neck. Scalp hair is also important in social communication.

Other human hair is involved in sexual communication (reviewed [52]). Puberty is signalled by the development of pubic and axillary hair in both sexes (Fig. 2.3), while the sexually mature man exhibits masculinity by developing a beard and greater body hair on the chest, upper pubic triangle and limbs. The beard's strong signal and its potential involvement in threatening display behaviour, like the lion's mane, may explain its common removal in the less openly aggressive industrialized countries. Human hair's important communication roles explain the serious psychological consequences and negative impact on the quality of life seen in hair disorders including androgenetic alopecia [14].

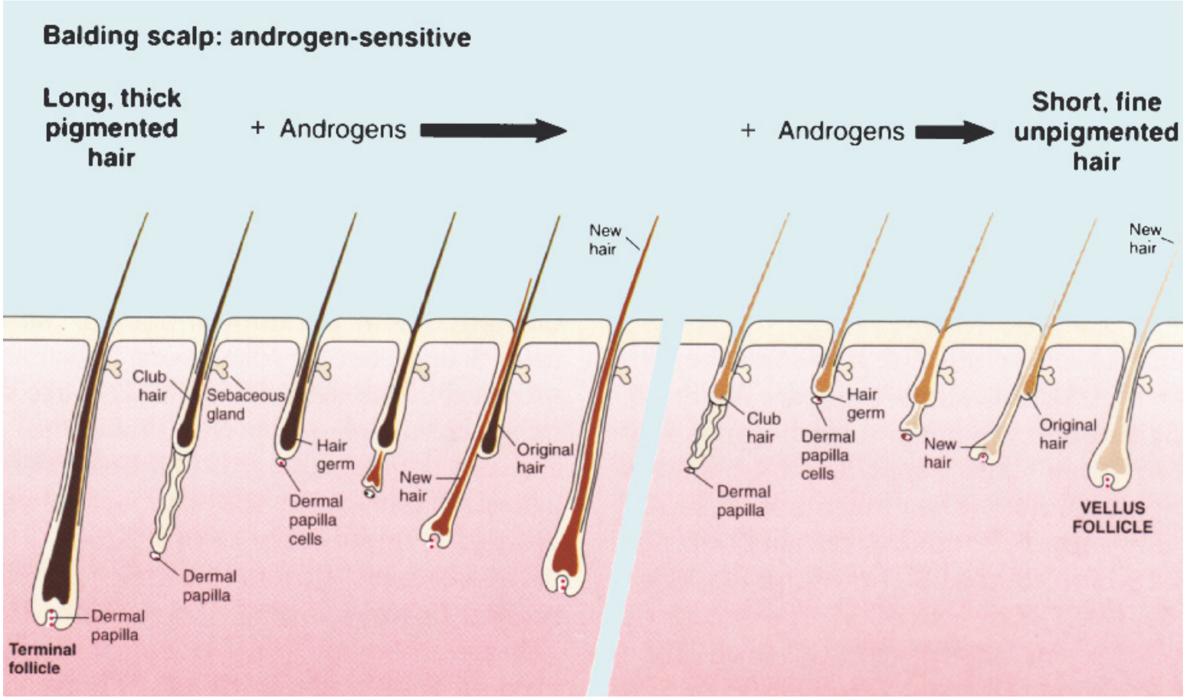


Fig. 2.1 Diagram of two hair follicle growth cycles where androgens cause the follicle and the hair it produces to become smaller. The gap between them represents other cycles not drawn. Hair follicles pass through regular cycles of growth (anagen), regression (catagen) and rest (telogen) during which the lower part of the follicle is regenerated and a new hair formed [29]. This permits the follicle to produce a different type of hair in response to hormonal stimuli to co-ordinate responses to changes such as sexual maturity or season. The new hair may differ in size and/or colour. The regenerated scalp hair follicles illustrated have responded to androgens by becoming smaller, protruding less far into the dermis and producing a smaller, less pigmented hair. Reproduced from Randall [48]

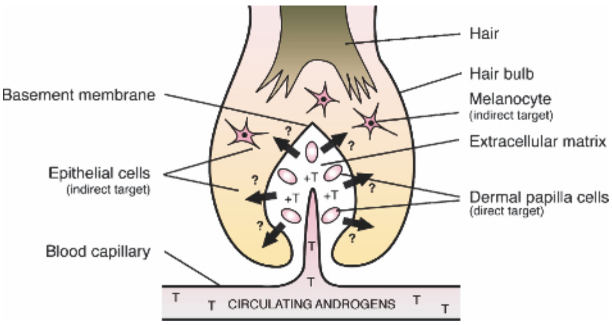


Fig. 2.2 Model of androgen action in the hair follicle. In the current model androgens from the blood enter the hair follicle via the dermal papilla's blood supply. They are bound by androgen receptors in the dermal papilla cells causing changes in the cell's production of regulatory paracrine factors; these then alter the activity of dermal papilla cells, follicular keratinocytes and melanocytes. (T Testosterone, ? unknown paracrine factors.) Reproduced from Randall [48]

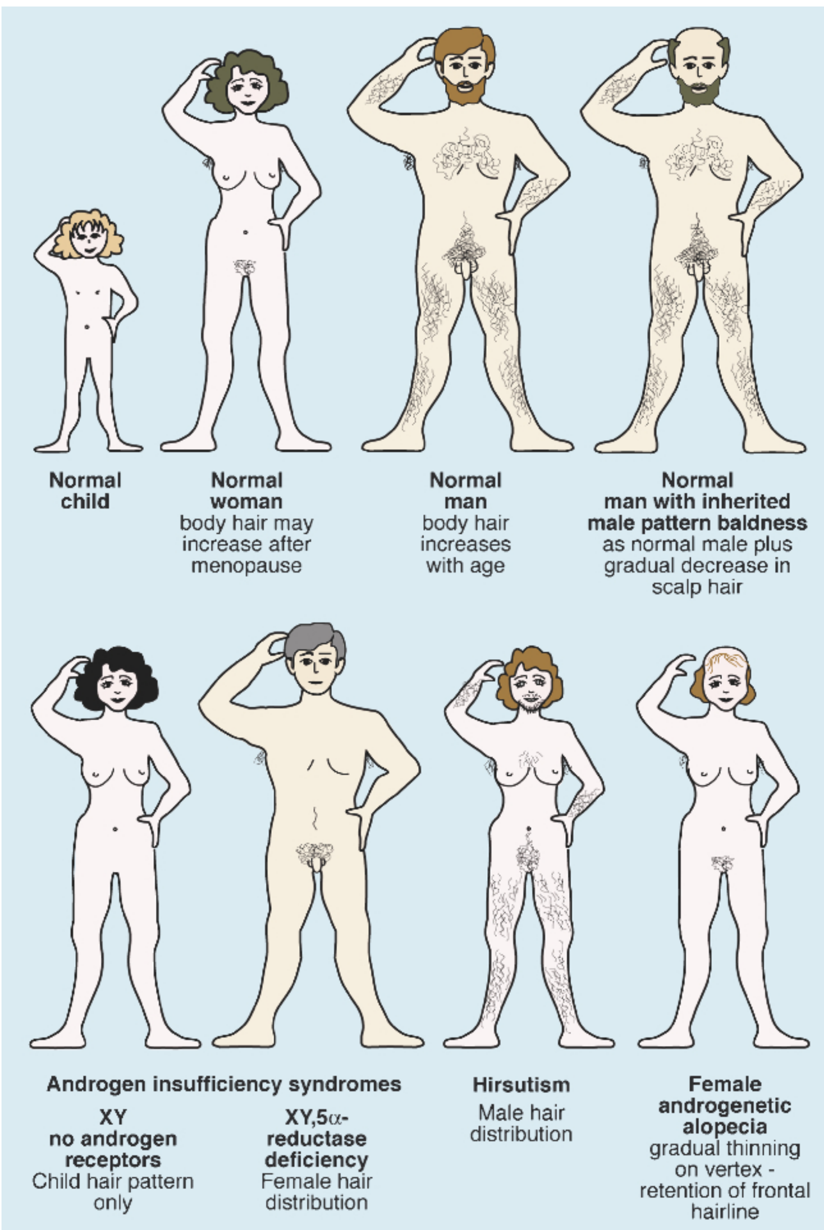


Fig. 2.3 Human hair distribution under differing endocrine conditions. Visible (i.e. terminal) hair with protective functions normally develops in children on the scalp, eyelashes and eyebrows. During, and after, puberty additional terminal hair develops on the axilla and pubis in both sexes and on the face, chest, back and limbs in men. In people with the appropriate genetic tendency, androgens may also stimulate hair loss from the scalp in a patterned manner causing androgenetic alopecia. People with various androgen insufficiency syndromes (*lower panel*) demonstrate that none of this occurs without functional androgen receptors and that only the axillary and the female pattern of lower pubic triangle hairs are formed in the absence of 5α-reductase type 2. Male pattern hair growth (hirsutism) occurs in women with abnormalities of plasma androgens or from idiopathic causes and women may also develop a form of female androgenetic alopecia. Reproduced from Randall [48]

2.3.2 Changing the Type of Hair by the Hair Follicle Growth Cycle

To fulfil all these roles the hair produced by a follicle often needs to be changed via the follicle's unique mechanism, the hair cycle (see Chap. 1). This involves destruction of the original lower follicle and its regeneration into another form which can produce a hair with different characteristics (Fig. 2.1). Exactly how different in size a hair can be to its immediate predecessor is currently unclear because many changes, such as production of a full beard or ear canal hair, take place over many years [17]. During each follicle's frequent cycles hairs are produced in anagen, the growth phase [29]. Cell division takes place in the matrix of the hair bulb outside the dermal papilla, after which the keratinocytes move up into the thinner part of the follicle, differentiating into the layers of the hair and its surrounding sheaths. Melanocytes in the bulb also transfer pigment to the hair keratinocytes to give the hair colour. Anagen is followed by a short regression phase, catagen, when the fully keratinized "club" hair moves up in the skin and the lower follicle rests in telogen. When telogen ends the dermal papilla cells and associated keratinocyte stem cells reactivate, a new lower follicle develops and a new hair grows up into the base of the upper follicle; the existing hair is generally lost, either by the physical movement of the new hair or a further active shedding stage, exogen.

The new hair may be very similar to its predecessor, like most human scalp hair, or may differ quite markedly, e.g. the brown summer and white winter hairs of arctic mammals or the Scottish mountain hare [52]. The type of hair produced depends on the regulatory dermal papilla [60] although the detailed cell biology and biochemistry of the local interactions are not fully understood. What is clear is that hair length is generally determined by the length of the anagen phase of the hair cycle; long scalp hairs are produced by follicles with anagen lasting over 2 years, while short finger hairs grow only for around 2 months [63]. This is, therefore, one of the main aspects regulated by hormones.

2.4 Endocrine Regulation of Seasonal Changes in Hair Growth

Hair follicles are under hormonal regulation, which brings about important co-ordinated changes in the insulative and colour properties of a mammal's coat in response to the environment, or in hair visibility to sexual maturity. Seasonal changes usually occur twice a year in temperate regions, with co-ordinated waves of growth and moulting to produce a thicker, warmer winter coat and a shorter summer pelage [9, 31]. These changes are linked to day length and, to a lesser extent, to temperature in the same way as seasonal breeding activity (reviewed [52]).

2.4.1 Animals

Long daylight hours initiate short periods of daily melatonin secretion by the pineal gland and the summer coat in many species, while short (winter) day length increases melatonin secretion and a longer, warmer winter pelage develops [9, 52, 63]. The pineal gland acts as a neuroendocrine transducer converting nerve impulses stimulated by daylight to reduced secretion of melatonin, normally secreted in the dark. Melatonin signals are generally translated to the follicle via the hypothalamus–pituitary route, although melatonin appears also to act directly on prolactin secretion by the pituitary [31]. Prolactin is strongly implicated in follicular seasonal changes, although it is unable to carry out full hormonal cyclic regulation in the absence of other pituitary hormones or the hormones they regulate in other endocrine organs, e.g. the gonadotrophins and sex steroids; insulin-like growth factor-1 (IGF-1) may also be involved (reviewed [52]). Increased circulating prolactin levels in periods of long daylight correspond to low summer hair growth, while the low prolactin concentrations observed in short days correspond with increased winter hair growth in many species. Prolactin receptors are seen in rodent and mink skin and the key dermal papilla and sheep hair follicles and infusion of local prolactin in vivo also inhibits local hair growth in goats. Interestingly, prolactin messenger ribonucleic acid (mRNA) is also expressed in hair follicles of several species suggesting that prolactin is produced as a local paracrine factor.

Other hormones implicated in regulation of the hair growth cycle include the sex and adrenal steroids, which delay anagen in rats (whereas gonadectomy and adrenalectomy advance it), and thyroid hormones, which advance anagen [9, 52]. Interest in oestrogen's effects on hair growth has reactivated recently. Topical, i.e. external, application of 17β-oestradiol to mice skin inhibits hair growth and accelerates catagen, while antioestrogens promote early anagen [4, 41]. Oestrogen receptors alpha (ERα) and beta (ERβ) have been located in human hair follicles [69] and cultured dermal papilla cells by immunocytochemistry and reverse transcriptase polymerase chain reaction (RT-PCR) [68]. How all these circulating hormones interact is still not clear, but the main drivers of light, melatonin and prolactin are now well established in the control of seasonal coat changes.

2.4.2 Seasonal Variations in Human Hair Growth

Seasonal changes are less obvious in human beings, where follicle cycles are generally not synchronized with their neighbours except in local groups of three follicles called Demeijère trios [63]. Regular annual cycles in human scalp and beard and other body hair have only been fully recognized relatively recently [7, 42, 53]. Men and women in northern temperate regions exhibit an autumnal moult of scalp hair. Since scalp hair usually grows for 2–3 years or longer [29, 63], it is remarkable that any annual cycle is apparent at all. Randall and Ebling [53] found that beard and thigh hair growth rate was low in the winter in 14 Caucasian men, but increased significantly in the summer (Fig. 2.4). Similar summer peaks of semen volume, sperm count and sperm mobility were reported in 260 French men [58], whose luteinizing hormone (LH), testosterone and 17β-oestradiol levels peaked in the autumn; smaller studies also reported low testosterone in the winter and higher levels in summer in European men and pubertal boys (reviewed [17]). Testosterone changes probably alter beard and thigh hair-growth rate, but whether they regulate scalp follicles is less clear as most scalp hair growth is not androgen-dependent and seasonal effects are also seen in women. However, androgens do inhibit scalp follicles in certain areas of genetically susceptible individuals, causing balding [16], and low levels of androgen receptors are present in cultured dermal papilla cells [57] derived from non-balding scalp follicles, making such a response feasible.

In contrast to single annual cycles on the scalp and beard, there are biannual changes in the number of follicles actually growing hair on the thigh [17]. This biannual pattern resembles the spring and autumn moults seen in many temperate mammals and may remain from earlier in our evolution. Presumably these cycles are controlled in a similar way to those described in Sect. 2.4.1 for other mammals. Human beings do retain the ability to respond to changes in day length by altered secretion of melatonin, prolactin and cortisol, but urban environments in which light and dark are artificially manipulated probably suppress these responses [73]. Nevertheless, people living in the Arctic and those with seasonal affective disorder maintain melatonin rhythms and our study population definitely maintained seasonal behaviour patterns (reviewed [52]).

In addition to demonstrating that human beings in temperate zones are still seasonal mammals, these pronounced annual changes have an important significance for any investigations of human scalp or androgen-dependent hair growth. These are parameters which are often measured in assessments of new therapies; to be accurate measurements should be carried out over a full year, otherwise results will be very difficult to interpret due to the endogenous variation.

2.5 Hormonal Regulation of Human Hair Growth

Apart from the seasonal changes described in Sect. 2.4.2, the most obvious regulators of human hair growth are the androgens, as long as an individual has good nutrition and normal thyroid function (reviewed [52]); hypothyroidism is normally associated with hair loss [10]. Pregnancy also has effects on hair growth with diffuse hair loss after the birth, a well established clinical phenomenon.

2.5.1 Effects of Pregnancy

Lynfield [34] found that more scalp follicles were in anagen during the second and third trimesters of pregnancy (95%) and for about a week after the birth. By 6 weeks this had fallen to only about 76% and remained low for 3 months. Pregnancy hormones maintain follicles in anagen, but after the birth many enter catagen and telogen, resulting in a synchronized partial shedding or moult. This is likely to be particularly noticeable if it coincides with the autumnal increase in shedding (Sect. 2.4.2). Which hormones are involved is uncertain, although oestrogens and prolactin are possibilities and human follicles have receptors for both prolactin [13] and 17β-oestradiol [68, 69]. However, 17β-oestradiol inhibits hair growth and accelerates the start of catagen in rodents [4, 41], and inhibits cultured scalp follicles [6], the opposite effect to pregnancy. Prolactin also inhibits cultured human follicles [13], which could support a role in post-partum shedding.

2.5.2 The Paradoxical Effects of Androgens on Human Hair Follicles

Androgens' dramatic stimulation of human hair growth manifests initially in puberty with the development of pubic and axillary hair in both sexes [35, 36], occurring later in boys than girls in parallel with rising plasma androgens. Further evidence comes from testosterone's ability to stimulate beard growth in eunuchs and elderly men [5], and the inhibition of beard [17] and male pattern baldness [18] by castration. However, the strongest support comes from individuals with complete androgen insufficiency, i.e. without functional androgen receptors [38]. These XY individuals develop a female phenotype, as they are unable to respond to androgen.

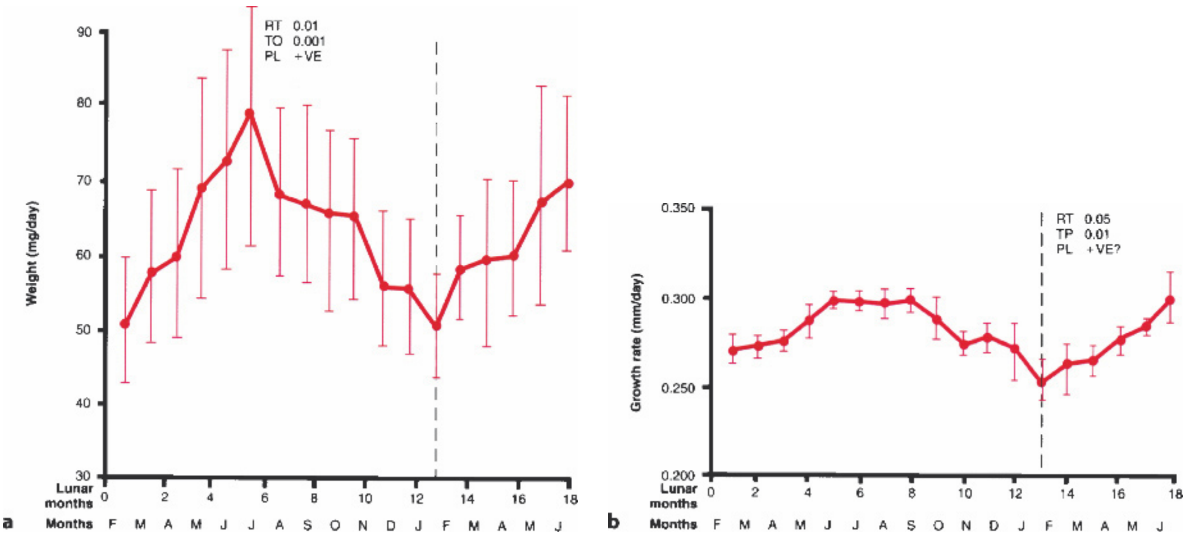


Fig. 2.4a,b Seasonal changes in androgen-dependent human hair growth. British men exhibit marked seasonal changes in hair growth in several parts of the body [53]. Beard (**a**) and thigh hair (**b**) grows significantly faster in the summer months and more slowly in the winter, even when the men have indoor occupations. Measurements are the mean ±SEM for Caucasian men (13 beard, 14 thigh) from northern England. Statistical analysis was carried out using runs (RT), turning points (TP) and phase length (PL) tests. Data from Randall and Ebling [53], redrawn for [50]

However, their female phenotype is incomplete as they do not develop even female patterns of pubic or axillary hair (Fig. 2.3, lower panel). Growth hormone is also required for the full androgen response, as sexual hair development is inhibited in growth hormone deficiency (see [52]).

Androgens stimulate the tiny vellus follicles that produce fine, virtually colourless and almost invisible hairs to transform into larger, deeper follicles forming longer, thicker, more pigmented hairs (Fig. 2.5, upper panel); they do this by passing through the hair cycle to regenerate a new follicle to carry out such changes (Fig. 2.1). Although androgens stimulate hair growth in many areas, being responsible for the greater amount of body hair on the face, upper pubic diamond, chest and limbs, etc. in adult men [17], they can also have the opposite effect on specific areas of the scalp, often in the same individual, causing loss of terminal hair and balding [16]. This involves the reverse transformation of the large, deep follicles that produce very long, often heavily pigmented terminal scalp hairs to miniaturized vellus follicles that form tiny, almost invisible hairs (Figs. 2.1, 2.5). This usually occurs in a precise pattern starting with regression on the forehead and thinning in the centre of the vertex and may continue to expose large areas of scalp [16]; the lower sides and back of the scalp normally retain terminal hair (Fig. 2.3, upper panel). Androgenetic alopecia is reviewed Chap. 9 and elsewhere [51]. Similar hair loss, which is considered androgen-dependent, can occur in women, but the pattern differs (Chap. 10). In women, the frontal hairline is normally retained and progressive generalized thinning occurs on the vertex until it appears bald [33]. In contrast, androgens appear to have no effect on other hairs such as the eyelashes. This is a biological paradox. How does one hormone stimulate the hair follicle in many areas, have no effect in another, while causing inhibition in the same organ in a different part of the body, often in the same individual?

Interestingly, there are other differences between follicles which all respond to androgens with increased growth. Axillary and lower pubic follicles enlarge in response to female levels of androgens, while other follicles require male levels [35, 36]. Follicles also differ in their sensitivity, or speed of response. In boys and hirsute women facial follicles alter initially above the mouth and on the chin; eventually this spreads over the face and parts of the neck [35, 36]. This progression resembles the patterned progression of androgenetic alopecia. Many androgen responses are gradual, with some follicles taking years to manifest their full response. Beard weight increases dramatically during puberty but continues to rise until the mid-thirties, while terminal hairs may only be visible on the chest or external ear canal years after puberty [17]; the miniaturization processes of androgenetic alopecia also continue well into old age [16]. This delay parallels the late onset of

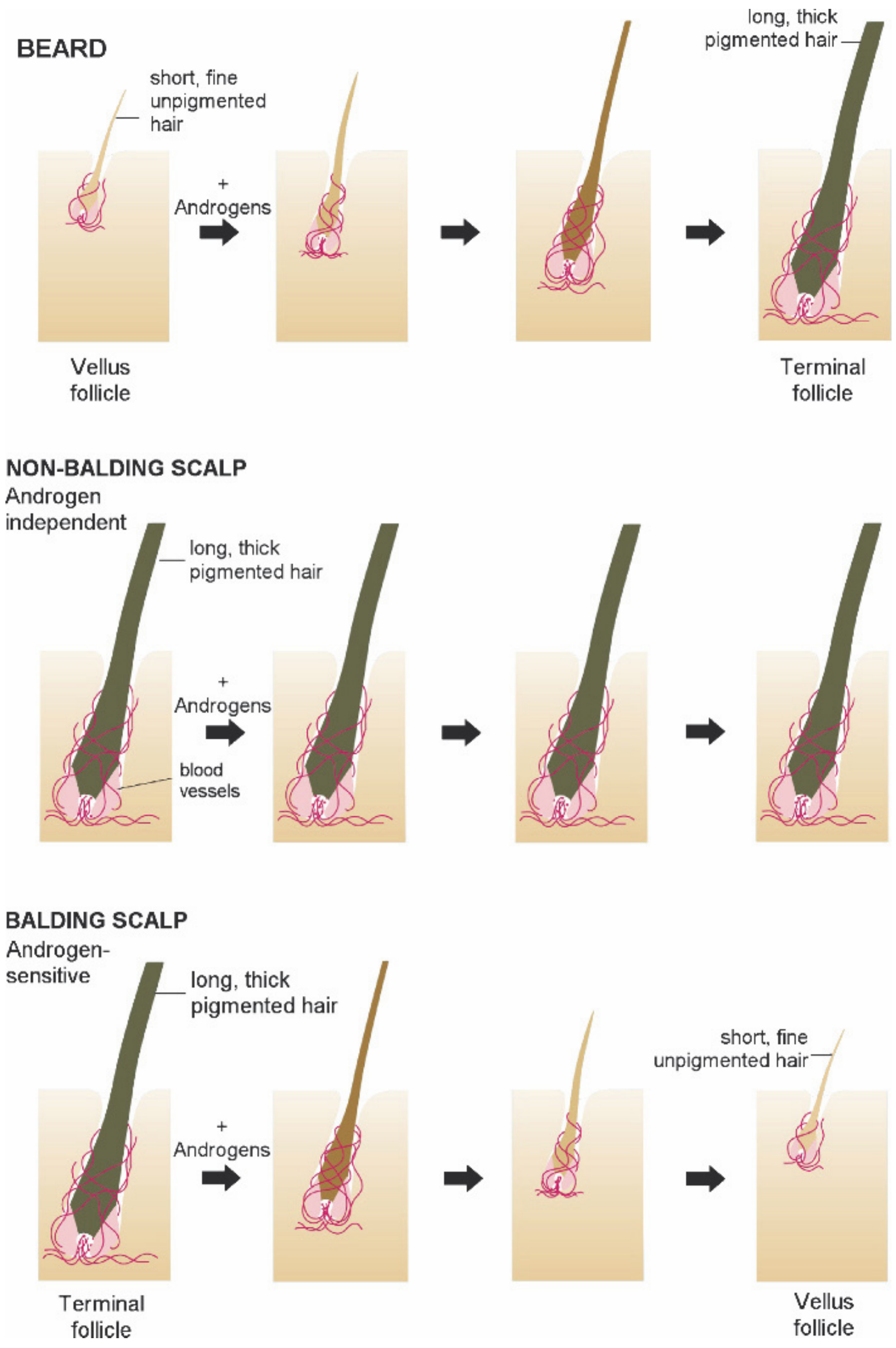


Fig. 2.5 Androgens have paradoxically different effects on human hair follicles depending on their body site. During and after puberty androgens stimulate the gradual transformation of small follicles producing tiny, virtually colourless, vellus hairs to terminal follicles producing longer, thicker and more pigmented hairs (*upper panel*) [8]. These changes involve passing through the hair cycle (see Fig. 2.1). At the same time many follicles in the scalp and in the eyelashes continue to produce the same type of hairs, apparently unaffected by androgens (*middle panel*). In complete contrast, androgens may inhibit follicles on specific areas of the scalp in genetically susceptible individuals causing the reverse transformation of terminal follicles to *vellus* ones and androgenetic alopecia [16]. Diagram reproduced from Randall [48]

androgen-dependent benign prostatic hypertrophy and prostatic carcinoma.

Another demonstration of the individual behaviour of follicles from different sites is the contrasting growth patterns of beard and axillary hair. Although both increase rapidly during puberty in Caucasians and Japanese men, beard growth remains heavy into old age, while axillary hair growth falls rapidly in both sexes and races after the mid-twenties [17]. This is another paradox: why do follicles in some areas no longer show their androgenic responses, while in many others they maintain or extend them?

All these contrasts must be due to intrinsic differences in gene expression within follicles at different sites, since all are exposed to the same circulating hormones. A follicle's retention of its original androgen response when transplanted confirms this [43]. Presumably, this genetic programming occurs during the patterning processes during development. The molecular mechanisms involved in the formation of different types of follicles during embryogenesis are not clear, but may include secreted signalling factors, such as Eda, sonic hedgehog, Wnt and various growth factor families (e.g. the BMPs), nuclear factors (including various homeobox genes), and others such as Hairless and Tabby, plus transmembrane and extracellular matrix molecules [40, 75].

Human follicles need androgen exposure not only for the initial transformations, but also to maintain many effects. If men are castrated, beard growth falls but neither beard growth nor male pattern baldness returns to prepubertal levels [16, 17], suggesting that some of the altered gene expression does not require androgens to maintain its effects. However, beard growth is enhanced in the summer, probably in response to increased circulating androgens (Sect. 2.4.2), antiandrogen treatment reduces hair growth in hirsutism and another blocker of androgen action, the 5α-reductase type 2 inhibitor finasteride, can cause regrowth in androgenetic alopecia [28]. This suggests that androgens are required to maintain most of the response, as well as to initiate progression.

The intrinsic differences in hair follicle responses to androgens depending on their body site have an important consequence for anyone wishing to investigate androgen action in human follicles. It is essential to study follicles which respond appropriately in vivo for the question being addressed. Unfortunately, this means that the most usually available material, non-balding scalp, is inappropriate for many experiments.

Genetics play important roles in androgen-dependent hair growth (reviewed [52]). Male pattern baldness and heavy beard growth run in families: Caucasians generally have greater hair growth than the Japanese, despite similar testosterone levels, and men of African descent exhibit much less androgenetic alopecia. Interestingly, both women with polycystic ovaries and their brothers with early androgenetic alopecia showed a link to one allele of the steroid metabolism gene, CYP17 [3]. However, no association was seen in men with androgenetic alopecia and genetic markers for the genes for 5α-reductase enzymes involved in metabolizing testosterone to the more potent 5α-dihydrotestosterone. Some changes in the androgen receptor were more frequent in balding men [12] and androgen receptors from girls with precocious puberty, i.e. early pubic hair, showed a smaller number of CAG repeats than controls [23]. Whether this has functional significance such as increased androgen sensitivity or simply reflects linkage disequilibrium with a causative mutation is unclear. However, the similar steroid-binding capacity of androgen receptors from balding and non-balding follicle dermal papilla cells does not support increased sensitivity [20].

2.5.3 How Do Androgens Carry Out These Changes?

Androgens have to alter many aspects of follicular cell activity to change the type of hair produced. They have to change the division capacity of epithelial matrix cells, determine whether they should differentiate into medulla (a central part of the hair found in large hairs) and regulate the amount of pigment that is produced by the follicular melanocytes and/or transferred to the differentiating keratinocytes to determine hair colour. They also have to alter dermal papilla size, since this maintains a constant proportion to the hair size [11, 72], and the connective tissue or dermal sheath, which surrounds the follicle, must expand to accommodate a larger follicle. Androgens definitely alter these aspects of hair follicle activity, as antiandrogen treatment reduces diameter, rate of growth, hair length, pigmentation and medullation in hirsute women [64], whereas blocking 5α-reductase activity increases many aspects in androgenetic alopecia [28]. The remaining question is whether androgens act on each target cell individually or through one co-coordinating system with indirect effects on other cell types.

2.5.3.1 Current Model for the Action of Androgens in Hair Follicles

Since androgen-potentiated changes are complex but there is little evidence of abnormalities, the processes must be highly controlled. This suggests that androgen action is co-coordinated through one part of the follicle. The current hypothesis, proposed in the early 1990s [56] (reviewed [46, 50, 52]), focuses on the dermal papilla. In this androgens act directly on the dermal papilla cells, binding to their androgen receptors and initiating al-

tered gene expression of regulatory factors which influence the other target cells (Fig. 2.2); these factors could be soluble paracrine factors and/or extracellular matrix factors. This model makes the dermal papilla the key direct target, while other cells such as keratinocytes and melanocytes are indirect androgen targets.

Some recent observations suggest minor modifications to this model. The dermal sheath which surrounds the hair follicle is now thought to play an important role in the hair follicle. The lower sheath can form a new dermal papilla and stimulate new hair follicle development [61]. Cultured dermal sheath cells from beard follicles contain similar levels of androgen receptors to beard dermal papilla cells (Merrick et al. unpublished observations) and balding scalp dermal sheath also expresses the mRNA for 5α-reductase type 2 [2]. The sheath may function as a reserve to replace the key inductive and controlling role of dermal papilla cells if they are lost, because of the essential role of hair for survival in many mammals. Dermal sheath cells may also respond directly to androgens to facilitate alterations in sheath, or even dermal papilla, size in the formation of a new anagen follicle.

Recently, a very specialized keratin, hHa7, was found in the central medulla of beard, pubic and axillary hairs [27]. Beard medulla cells showed co-expression of keratin hHa7 and the androgen receptor. Since the hHa7 gene promoter also contained sequences with high homology to the androgen response element (ARE), keratin hHa7 may be regulated by androgens. However, when the promoter was transfected into prostate cells there was no stimulation. Although this could be due to inhibitors in the prostate cells, keratin hHa7 with the same promoter is also expressed in androgen-insensitive body hairs of chimpanzees [27]. The full significance of these observations is not yet clear, but androgens may also stimulate medullary cells directly. These results merit a modification of the model to include a possible specific, direct action of androgens on the cells of the lower dermal sheath and medulla cells.

2.5.3.2 Mechanism of Androgen Action in Hair Follicles

Androgens, like other steroid hormones, act on target cells by diffusing through the plasma membrane and binding to specific intracellular receptors (Fig. 2.6). On binding the relevant steroid, the receptor complexes undergo a conformational change exposing DNA binding sites and, often in association with accessory proteins and co-factors, bind to specific hormone response elements (HRE) in the DNA, promoting the expression of specific, hormone-regulated genes [19]. The mechanism for androgens is more complex than those of other steroids. In some tissues, such as skeletal muscle, testosterone, the main circulating androgen in men, binds the receptor. However, in many tissues, including the secondary sexual tissues such as the prostate, testosterone is metabolized intracellularly by one of the 5α-reductase enzymes to 5α-dihydrotestosterone, a more potent androgen, which binds preferentially and more strongly to the androgen receptor to activate gene expression [47] (Fig. 2.6).

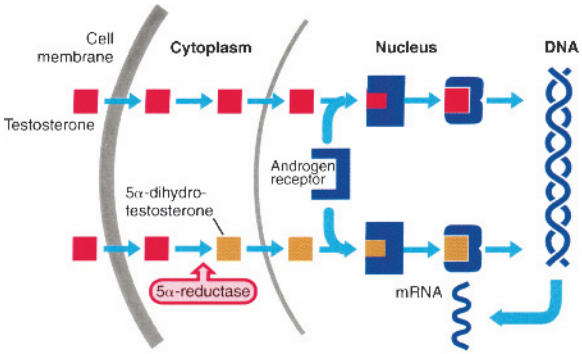


Fig. 2.6 Simple schematic of the general mechanism of androgen action. Androgens diffuse from the blood through the plasma membrane. Inside the cell, like other steroid hormones, testosterone may bind to specific androgen receptors (*upper scheme*). This appears to occur in many tissues such as skeletal muscle and axillary and pubic hair follicles. However, in certain tissues, particularly the secondary sexual organs such as prostate or beard and balding hair follicles, testosterone is metabolized to the more potent androgen 5α-dihydrotestosterone (*lower scheme*). If both are available in similar quantities the receptor will bind 5α-dihydrotestosterone. Once hormone has bound, the receptor complex undergoes a conformational change exposing DNA binding sites and the hormone-receptor complex, in conjunction with other co-activating proteins, will bind to specific hormone response elements (*HREs*) in the DNA altering the expression of specific androgen-dependent genes

All androgen-dependent follicles require the androgen receptor to respond, as demonstrated by the absence of adult body hair in complete androgen insensitivity (Fig. 2.3), the natural human "knock-out" model for the androgen receptor [38]. In contrast, the need for 5α-reductase activity varies with follicle site. Individuals with 5α-reductase type 2 deficiency only produce female patterns of pubic and axillary hair growth after puberty, although their body shapes become masculinized [74] (Fig. 2.3); 5α-reductase type 1 deficiency has never been reported. This suggests that 5α-dihydrotestosterone is

necessary for the responses of all the male-specific hair follicles including the beard, chest and upper pubic triangle, while testosterone itself can stimulate the axilla and lower pubic triangle follicles characteristic of adult women. Since people with 5α-reductase type 2 deficiency do not show androgenetic alopecia and the 5α-reductase type 2 inhibitor, finasteride, can restore hair growth in male pattern baldness [28], 5α-reductase type 2 also seems to be important for androgen-related balding.

It is unclear why some follicles need 5α-dihydrotestosterone while others need testosterone to carry out the alterations in gene expression required to cause the same types of cell biological changes that lead to a larger hair; it seems likely that the cells use different intracellular coactivating proteins to act with the receptor. This is yet another paradox of androgen action in human hair follicles. The skin and hair follicles contain a range of enzymes that can metabolize weak androgens, such as circulating dehydroepiandrosterone from the adrenals, to the more powerful testosterone, or potent androgens such as testosterone and 5α-dihydrotestosterone to the oestrogens 17β-oestradiol or oestrone (see Fig. 2.7). The lack of hair in complete androgen insufficiency syndrome demonstrates that the androgen receptor is crucial for such hair growth; therefore, the androgens that bind most strongly to the receptor, namely testosterone and 5α-dihydrotestosterone, must be the most important.

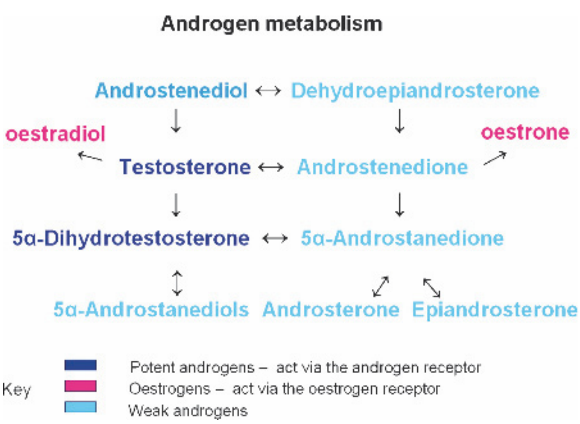


Fig. 2.7 Androgen metabolism. Circulating androgens such as testosterone from the testis in men and weaker androgens such as dehydroepiandrosterone and androstenedione from the adrenals and ovaries in women can be metabolized in many skin tissues. Some metabolism causes an increase in potency, e.g. from testosterone to 5α-dihydrotestosterone, as the androgen receptor binds 5α-dihydrotestosterone more strongly even than testosterone, another potent androgen. Other metabolisms form weaker androgens normally involved in excretion pathways, e.g. the androstanediols or steroids which act via the other steroid receptors, i.e. the oestrogens

2.5.4 Support for the Dermal Papilla-Based Model of Androgen Action

The key molecules for this model, androgen receptors, have been localized by immunohistochemistry in the dermal papilla and by protein binding assay in cultured dermal papilla cells derived from androgen-sensitive follicles such as the beard, balding scalp and red deer mane (reviewed [52]). Cells from androgen-sensitive sites contain higher levels of specific, saturable androgen receptors compared to androgen-insensitive non-balding scalp in vitro [1, 20, 57]. Most importantly, testosterone metabolism by cultured dermal papilla cells also reflects hair growth in patients with 5α-reductase deficiency; beard, but not pubic or non-balding scalp cells form 5α-dihydrotestosterone in vitro (reviewed [52]). This has led to wide acceptance of the hypothesis.

2.5.5 Paracrine Factors in Mesenchymal–Epithelial Interactions in Androgen-Regulated Hair Follicles

The final part of the model involves the alteration of paracrine signalling factors by dermal papilla cells. Cultured dermal papilla cells secrete extracellular matrix factors and also soluble, proteinaceous growth factors which stimulate the growth of other dermal papilla cells, outer root sheath cells and transformed epidermal keratinocytes (reviewed [52]). Soluble factors from human dermal papilla cells can cross the species divide and affect the growth of rodent cells in vitro and in vivo [15] (Fig. 2.8), paralleling the ability of human dermal papillae to induce hair growth in vivo when implanted into transacted follicles of athymic mice [26]. Importantly, physiological levels of testosterone in vitro increased the mitogenic capacity of beard cells to affect beard dermal papilla cells, outer root sheath cells and keratinocytes and decreased that of androgenetic alopecia dermal papilla cells from men and stump-tailed macaques in line with the hypothesis (reviewed in [52]). This implies that an autocrine mechanism of producing paracrine factors for beard cells is involved in androgen-stimulated beard cell growth. Certainly, the size of the dermal papilla is proportional to the size of the hair [11, 72] and androgen-mediated changes involve an alteration in dermal papilla cell numbers as well as the amount of extracellular matrix present [11]. A need to modify the autocrine production of growth factors after androgen stimulation

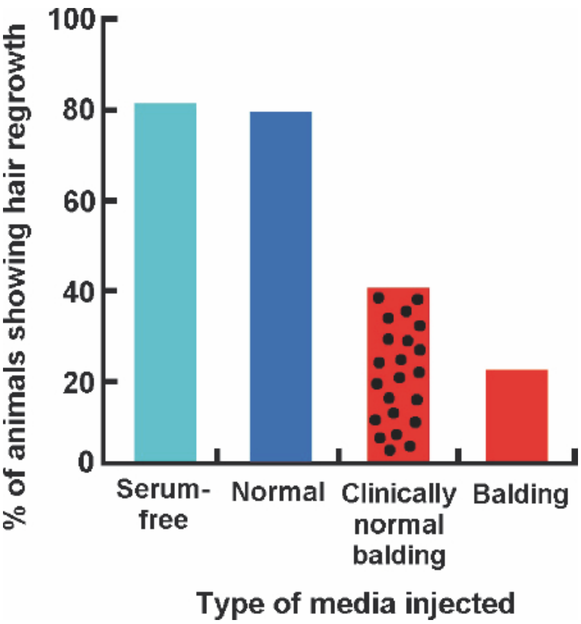


Fig. 2.8 Androgenetic alopecia dermal papilla cells secrete soluble factors in culture which delay rodent hair growth in vivo. Conditioned media produced by dermal papilla cells cultured from normal, lesional edges (termed *clinically normal*) and balding scalp hair follicles and control media were injected into mice (n=5 or 6) when the follicles were resting. Although normal dermal papilla cell media had little effect, media from both lesional edge and balding cells inhibited the start of anagen in the mice demonstrating an inhibitory effect caused by soluble factors produced by human dermal papilla cells which could cross the species divide. Data from Hamada and Randall [14]

could contribute to the slow androgenic response, which often takes many years to reach full effect.

As well as supporting the hypothesis for the mechanism of action, these results demonstrate that the paradoxical effects of androgen on hair follicles observed in vivo are reflected in vitro, strengthening the use of cultured dermal papilla cells as a model system for studying androgen action in vitro. The main priority now lies in identifying specific factors whose production is altered by androgens either in beard cells as an example of androgen-stimulated follicles or in androgenetic alopecia cells for inhibition effects. There is great interest in paracrine signalling in developing and cycling follicles (e.g. [59]), but to date only insulin-like growth factor (IGF-1) has been identified as secreted by beard dermal papilla cells under androgen stimulation in vitro [25]. IGF-1 is a potent mitogen and maintains anagen in cultured scalp follicles [45]; when its effects are blocked in the IGF-1-receptor-deficient mouse abnormal patterns of hair follicle growth and differentiation occur [32]. Stem cell factor (SCF, also known as mast cell growth factor, c-kit ligand or Steel factor) is secreted in greater quantities by beard than non-balding scalp cells, although androgens in vitro do not alter its production [21]. As SCF, the ligand for the melanocyte receptor c-kit, plays important roles in the development of epidermal and hair pigmentation, the dermal papilla may be the local source of SCF for follicle melanocytes. Beard cells' greater production of SCF indicates that in vivo androgens had increased *scf* gene expression by facial dermal papilla cells to cause the hair darkening seen when beard develops. DNA microarray methods, which facilitate comparison of the genes expressed under different conditions, also revealed different gene expression between beard and normal scalp dermal papilla cells, with three genes, *sfrp-2, mn1* and *atp1β1*, expressed at higher levels in beard cells, but no changes due to androgen in vitro [62].

Although dermal papilla cells from androgenetic alopecia areas are even more difficult to culture than those from normal scalp follicles [54], studies using these cells have also produced some interesting results. Androgens inhibit gene expression of the protease nexin-1 in cells derived from balding hair follicles [65]. Protease nexin-1, also known as glia-derived nexin-1, is a potent inhibitor of serine proteases such as thrombin, urokinase and plasmin, thereby regulating cellular growth and differentiation in many tissues. Since its effect in other tissues is modulated by extracellular matrix components such as type IV collagen, which dermal papilla cells also produce, alterations in protease nexin-1 production by dermal papilla cells could change their production of such extracellular matrix components and therefore the size of the follicle and hair produced. Androgens also stimulate the production of another commonly inhibitory factor, transforming growth factor-β (TGF-β), by a line of cultured androgenetic alopecia dermal papilla cells with "knocked-in" androgen receptors [24], and of TGF-β2 by two of four natural androgenetic alopecia cells [22]. TGF-β is a strong candidate for a role in inhibiting keratinocyte activity in androgenetic alopecia (reviewed in [52]). Follicular keratinocytes have receptors for TGF-β and it inhibits human hair follicle growth in vitro [44] and induces catagen in human beings and mice, while a probable suppressor of TGF-β1 delays catagen progression in mice in vivo. However, when gene expression in cultured dermal papilla cells was compared using DNA macroarray analysis TGF-β2 and TNF-α were actually slightly reduced in balding cells [39]. This could reflect the limitations of using a single control sample of non-balding dermal papilla cells for a comparison with cells from four people with androgenetic alopecia.

Media conditioned by dermal papilla cells from balding scalp follicles also inhibited the growth of both human and rodent whisker dermal papilla cells in vitro and delayed mouse hair growth in vivo (Fig. 2.8) [15]. The results suggest the active secretion of an inhibitory factor or factors. Transforming growth factor β is unlikely to be involved as it is associated with the transition from anagen to catagen, it does not delay the onset of anagen, and receptors for TGF-β are only in follicular keratinocytes, not the dermal papilla cells responding here (reviewed [15, 52]). Another inhibitory factor, interferon-β, was secreted by a single line of SV-40 transformed normal scalp dermal papilla cells whose media suppressed the growth of outer root sheath cells [30]. However, the significance of this is unclear as these were normal scalp cells, not balding ones, and normal scalp medium usually stimulates cell growth. Further studies of paracrine factors produced by dermal papilla cells under androgen stimulation should clarify these control pathways and thus lead to better treatments.

2.5.6 Experimental Techniques

Studying androgen action in hair follicles is hampered by the lack of good, readily available and easy to use experimental models. Human hair follicles are the best tissue for investigating androgen mechanisms of action, but it is not ethical to carry out much research on people other than noninvasive observations, e.g. studying seasonal changes, or clinical trials of new therapies. Unfortunately, there are also great difficulties when considering animal models for investigating androgen action (reviewed [55]). For example, the Wistar laboratory rat and the black mouse C57BL/6, used to study many aspects of hair growth, are not suitable for investigating androgen action because there are major differences in function and hormonal regulation between human beings and other mammals. The androgen-dependent manes of lions (*Panthera leo*) and red deer (*Cervus elaphus*) are the most likely mammalian parallels for a man's beard, but neither is practical for in vivo studies. More useful in vivo models include specialized androgen-sensitive follicles, such as those of the hamster costovertebral gland (a secondary sexual tissue involved in social communication), and mice with immunological deficiencies, e.g. nude (Foxn1nu/Foxn1nu) mice, which are unable to reject foreign skin and are used in special aseptic environments to accept human skin grafts from androgenetic alopecia [71]. Androgen-dependent hair loss in the androchronogenetic alopecia mouse [37] and, particularly, the stump-tailed macaque [70] has been harnessed to investigate novel treatments for androgenetic alopecia. However, both are somewhat different from human balding and the effect is seen in both sexes.

In vitro models generally offer the best opportunity to investigate human follicles since isolated cells, follicles or skin samples can be readily cultured from small samples of human skin. Limited amounts of human tissue are available for in vitro studies, but this is frequently a surgical by-product and may not be appropriate to answer particular questions such as how androgens act in follicles from different sites. Primary cultures of various individual cell types have been studied (reviewed [55]). These allow assessment of the features of individual cell types with or without manipulation in vitro, investigation of the interactions of the various cell types in vitro, or re-implantation of the cells in vivo in rats, nude mice or even people. Such studies have provided important information about the roles of dermal papilla cells and indicate that the dermal sheath can take over the inductive roles of the dermal papilla [61]. Such cultured cells have serious disadvantages including the short-lived nature of primary cultures, the absence of their normal cellular interactions, physical constraints and their natural environmental supplies of nutritive and regulatory factors. Some of these disadvantages are overcome by organ culture of isolated follicles [45], which achieves more normal cellular interactions between many cell types; the follicles can synthesize new hair in vitro, while still retaining the ability to be manipulated in vitro. However, these are still short-lived and the limited types of human follicles available have prevented this approach from being used much for androgen studies. Culture of whole skin biopsy samples theoretically overcomes the limitations on cellular interactions and physical constraints, but there are difficulties in ensuring penetration of nutrients, etc. and in understanding what is happening in which part of the skin.

Practical in vitro models for studying androgen action include human dermal papilla cells and similar cells and whole hair follicles from red deer, which have androgen-dependent manes. Red deer are killed for food and large numbers of follicles are available from one individual; follicle organ culture and dermal papilla cells have both been studied successfully [8, 67]. Fortunately, cultured human dermal papilla cells from hair follicles with different sensitivities to androgens offer a useful model with which to study the effects of androgens [55]: the dermal papilla cells play a central role; they can be grown from small samples of human tissue; they can stimulate hair growth in vivo at low passage numbers [60]; and they retain characteristics in vitro which reflect their responses to androgens in vivo.

2.6 Clinical Relevance and Conclusions, Outlook – Future Developments

Understanding the hormonal regulation of human hair growth has important relevance to the clinician as the most common hair disorders, androgenetic alopecia and hirsutism, are potentiated by androgens. All androgen effects need androgen receptors in the follicle and many, but not all, require the intracellular metabolism of testosterone to the more potent 5*α*-dihydrotestosterone. This means that antiandrogens should block all androgen effects on hair growth, while 5*α*-reductase inhibitors should be more selective at inhibiting beard growth and balding but not axillary or female patterns of hair growth. Antiandrogens have unacceptable side-effects in men and both antiandrogens and 5*α*-reductase inhibitors are contraindicated in women of child-bearing age as they may feminize a male fetus.

In the current model for androgen action, the mesenchyme-derived dermal papilla in the hair bulb plays a central role in responding to androgens by altering its production of paracrine regulators which coordinate changes in follicular cells such as the keratinocytes which make the hair. Future research needs to focus on identifying these paracrine factors; understanding these should enable the development of more specific, focused treatments for both men and women which could hopefully be applied topically to reduce side-effects. Recently, a successful response to a 5*α*-reductase inhibitor, finasteride, was related to the increased expression of IGF-1 by the dermal papilla during treatment [66]; this provides clinical evidence of the importance of dermal papilla-produced paracrine factors and emphasizes the key role of the dermal papilla in androgen action.

Summary for the Clinician

The hair follicle is a dynamic organ able to regenerate new and different hairs under hormonal regulation to coordinate hair type with season, age or sex. Androgens are the main regulator of human hair growth with paradoxical differences in follicular responses depending on their body site; these range from stimulation, e.g. beard, through no effect on eyelashes to inhibition on the scalp. Follicles retain these different responses when transplanted – the basis of corrective cosmetic surgery for androgenetic alopecia.

Androgens potentiate important hair disorders including hirsutism and androgenetic alopecia acting via intracellular androgen recep-tors and 5α-reductase type 2 enzymes to alter gene expression within the follicle. These conditions are currently difficult to treat due to the unacceptable broad side-effects of antiandrogens in men, which block all androgen actions. 5α-reductase inhibitors, such as finasteride, seem appropriate in men because they selectively reduce testosterone metabolism to the more potent 5α-dihydrotestosterone and therefore should only affect tissues such as beard and balding follicles and the prostate. Neither is suitable for women of reproductive age due to the risk of feminizing a male fetus. Further research on the local signalling molecules altered by androgens in the regulatory dermal papilla of androgen-sensitive follicles may identify more selective targets for new therapies. When investigating new treatments in patients investigators need to remember the seasonal changes in human hair growth which affect scalp and androgen-stimulated growth.

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Chapter 3

Neuroimmunology of the Hair Follicle

3

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Synonyms
neuroimmune mediation, neurobiology, psycho-neuroimmunology

Key Features

- Neural networks in contact with immune cells are dense around the hair follicle.
- The hair follicle produces and consumes neuroimmune mediators.
- Neural and immune networks and mediators fluctuate throughout the hair cycle.
- Neuroimmune interaction and mediators affect hair growth and disorders: they are turned on by environmental factors such as stress.
- Interference with neuroimmune action is a pharmacological target in hair disease management.

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3.1 Introduction

Despite its tiny size, the hair follicle (HF) is a complex organ that can regulate its cyclic growth and regression processes in a largely autonomous fashion through close communication between its epithelial and mesenchymal components [9, 47]. Hair research and pharmacologic intervention therefore focus mainly on local regulatory circuits, such as HF testosterone metabolism or growth-factor-activated pathways [16, 46]. Beyond its autonomous regulation of growth and regression however, the HF is located in an environment rich in structures and cells that connect local to systemic regulatory systems, such as the endocrine (Chap. 2) and the nervous and immune systems (Fig. 3.1) [20, 34, 39, 40]. Interaction of these systems with the HF and with each other leads to a strong impact on hair growth behavior.

Neuronal mediators such as the sensory neuropeptide substance P (SP), for example, can turn on or terminate hair growth control mechanisms, such as keratinocyte proliferation or neurogenic inflammation

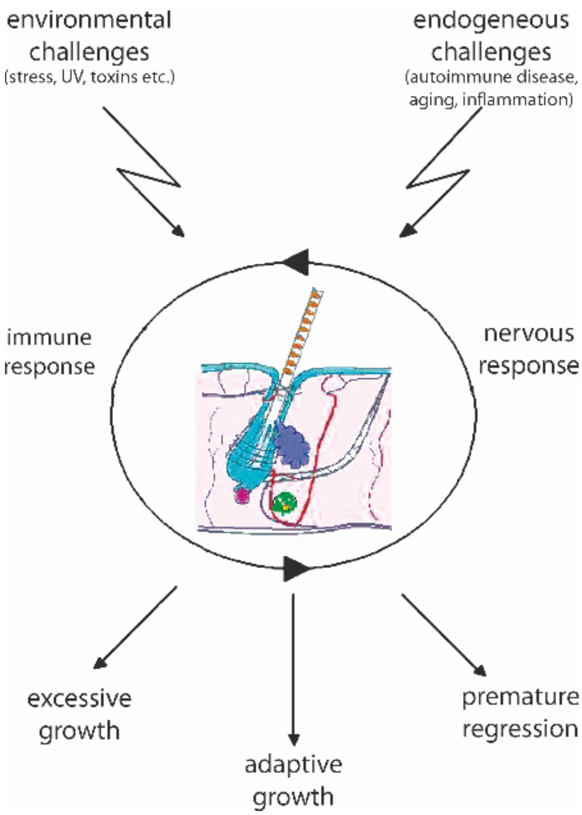


Fig. 3.1 The hair follicle is a target for systemic regulatory mechanisms involving the immune and nervous systems. This schematic figure depicts the hair follicle as an exemplary neuroimmune–mesenchymal–epithelial interaction system at the point between challenges and adaptive mechanisms

associated with HF regression [35, 39, 40]. At the same time, growth factors excreted by HF cells, such as the neurotrophin nerve growth factor (NGF), modulate the structure and function of their environment through, for example, perifollicular innervation, intra- and perifollicular immune cell populations, and neuroimmune communication [13, 37, 43].

In short, the HF and its local regulatory circuits depend on systemic mechanisms that can override local hair growth regulation and therefore they deserve close scrutiny, scientific appreciation, and pharmacologic targeting. Throughout this chapter we will focus on the HF as a model organ defined by lifelong plasticity of the accompanying immune cell populations and perifollicular innervation. This model may serve as an instructive blue-print for the analysis and understanding of neuroimmune regulation in epithelial tissue remodeling processes.

3.2 History

Our knowledge of the HF as a target for cutaneous nerve fibers and immune cells reaches back to the time when techniques to detect nerve fibers and immune cells in situ became available a century ago. Modern research approaches, in particular the development of transgenic mouse models and great advances in immunohistochemistry and molecular biology, have helped in the identification of a large array of candidates responsible for mediating pilo–neural–immuno interactions [14, 31, 39]. However, William Montagna's statement in his famous book *The Structure and Function of Skin* more than 30 years ago still holds true today:

"The largest sense organ of the body, interposed between the organism and its environment, skin must maintain that organism in a constant state of awareness of all environmental changes. ... Yet precious few of the problems that involve cutaneous innervation and specific cutaneous sensibilities have been solved, let alone the clinical problems that are in some way related to the peripheral nervous system."

Since the early 1990s, however, interdisciplinary research focusing on the nervous system and its interaction with the immune system has been constantly producing new perspectives and insights into neuroimmune regulatory mechanisms in healthy and diseased skin, many of which apply to hair growth.

3.3 Neuro–Immuno–Epithelial Interactions in Normal and Pathological Hair Growth

The HF is a densely innervated skin appendage, and relationships between the HF and its innervation are truly bi-directional: while neuromediators and neuropeptides are capable of influencing hair growth, HF keratinocytes produce NGF and other neurotrophic factors and induce remodeling of skin innervation in a hair-cycle-dependent manner [13]. The same is true for interactions between the HF and immune cells located nearby in the dermis and subcutaneous tissue. Keratinocytes in "healthy" HFs for example are protected from an attack by immune cells by their "immune privilege" characterized by low levels of major histocompatibility complex (MHC) class I/II antigens [33]. Below, we briefly summarize our current knowledge on the neuro–immuno–epithelial interactions during the normal hair cycle, as well as in a number of pathological skin conditions, such as the stress response and autoimmune hair loss [alopecia areata (AA)].

3.4 Structure and Function of HF Innervation

Nerve fibers that innervate HFs form two distinct neural networks: the first is located around the neck of the HF just underneath the epidermis and contains sensory C fibers along with sympathetic fibers, while the second is located around the permanent midsection of the HF between the isthmus of the sebaceous gland and the insertion of the arrector pili muscle into the HF and contains longitudinal Aδ fibers and circular C fibers (Fig. 3.2) [31, 39]. This latter localization is especially intriguing since it is near the HF stem cell region [16]. Both networks contain sensory nerve fibers, e.g., expressing calcitonin-gene related peptide (CGRP), and autonomic nerves expressing choline acetyl transferase (ChAT) [12, 35, 36]. Close by, the arrector pili muscle inserts into the hair follicle epithelium and nerve fiber bundles that give rise to additional noradrenergic and peptidergic nerve fibers innervating the muscle are regularly found nearby (Fig. 3.3).

In mice, the number of perifollicular nerves fluctuates very significantly during the hair cycle, increasing during early anagen and later decreasing during late anagen–catagen [11, 12, 35]. Substance P and the β_2-adrenoreceptor agonist isoproterenol accelerate anagen progression in murine skin organ culture, whereas

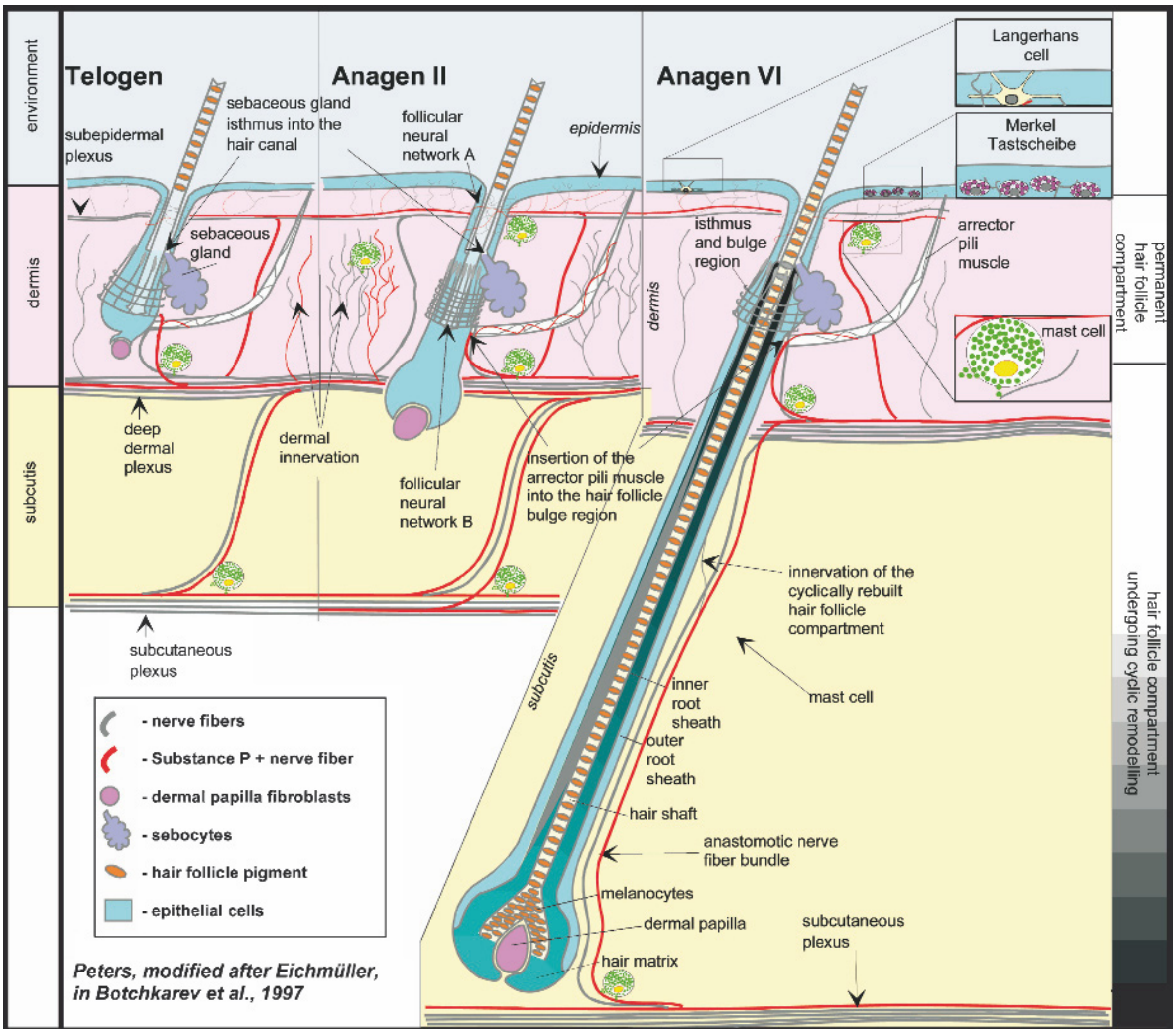


Fig. 3.2 The hair follicle is the target for systemic neuroimmune regulatory circuits. Hair follicles are densely innervated and their innervation keeps close contacts with immunocytes affecting the hair cycle, as described throughout the chapter. Please note the dramatic remodelling within the hair follicle compartment accompanied by neuronal plasticity

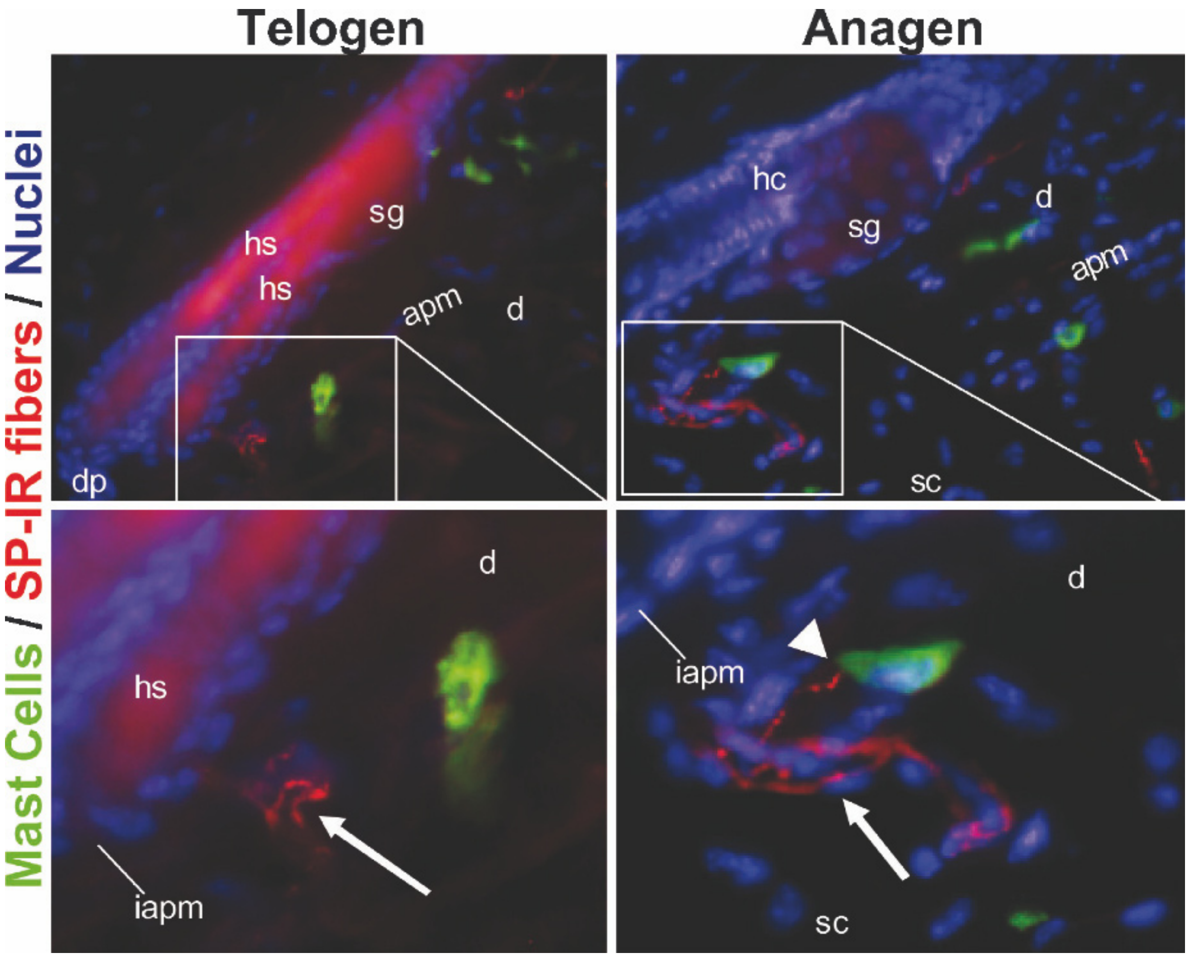


Fig. 3.3 Substance-P-immunoreactive nerve fibers and mast cell contacts during the murine hair cycle. Substance-P-immunoreactive (*IR* rhodamine immunofluorescence) nerve fibers are located in nerve fiber bundles at the border between the dermis (*d*) and subcutis (*sc*) region (*large arrows*) close to the bulge region of the hair follicle, where the arrector pili muscle (*apm,* not labelled, therefore only visible as background label and lined up nuclei) inserts (*iapm*) below the sebaceous gland (*sg*). Note the close contact between a single fiber and a mast cell (fluorescein fluorescence) in anagen skin. Cell nuclei are counterstained with DAPI. Note the dermal papilla (*dp*) at the dermis–subcutis border and the autofluorescence of the hair shaft (*hs*) in telogen and the missing hair shaft in the empty hair channel (*hc*) in early anagen

CGRP inhibits anagen promotion by SP [12, 35]. In turn, HF keratinocytes produce neurotrophins that influence perifollicular nerve fibers, inducing hair-cycle-dependent remodeling [13, 43]. In particular, during anagen HF keratinocytes produce predominantly NGF, while during catagen production of other neurotrophins [brain-derived neurotrophic factor (BDNF), neurotrophins-3 and -4 (NT-3, NT-4)] increases [13, 43]. Besides their effects on skin nerves, neurotrophins also influence hair cycle progression: NGF has stimulatory effects on anagen development, while all neurotrophins promote anagen–catagen transition and catagen progression, at least in part via binding to the p75 kD neurotrophin receptor (p75NTR), implicated in keratinocyte apoptosis [13, 37, 43].

3.5 Neuroimmune Regulatory Network Around Normal HFs

The epithelium of normal HFs is characterized by a relative immune privilege and expresses very low levels of MHC class I/II antigens accompanied by the local production of potent immunosuppressants [e.g., transforming growth factor-beta$_1$ (TGFβ_1) and alpha-

melanocyte-stimulating hormone (α-MSH)] [32, 33]. However, perifollicular nerve fibers that travel through the subepidermal and interfollicular dermis are located close to immune cells (macrophages, dendritic cells, mast cells) [40]. There is increasing evidence to suggest that neuroimmune interactions play an important role in the control of HF cycling (Fig. 3.4) [39].

Most often, skin nerve fibers form close contacts with mast cells [10, 38]. Peptidergic nerve fibers can communicate with mast cells through the release of neuronal mediators such as SP, CGRP, α-MSH, corticotrophin-releasing hormone (CRH), and many more [40]. Interestingly, these interactions also show hair-cycle-dependent changes, thus implicating the involvement of cross-talk between mast cells and nerves in hair growth regulation. Indeed, mast cell mediators are capable of stimulating anagen onset and progression, as well as promoting catagen [25, 26, 30].

In addition to mast cells, nerve fibers close to the HF contact dendritic cells. Here they may play an important role in the processing of antigen presentation [40]. Substance P, for example, can activate antigen presentation, while CGRP potently inhibits it. This last observation may explain why contact hypersensitivity is difficult to induce in mice that have all their HFs in the growth phase of the hair cycle, namely anagen. During this phase, CGRP-positive nerve fibers are present in high numbers in the murine back skin [35], facilitating contacts with Langerhans and other antigen-presenting cells.

3.6 Neuroimmune Interactions in Stress-Mediated Hair Growth Inhibition

In general, neuropeptide release from nerve fibers is considered to be pro-inflammatory and results in mast cell degranulation and the release of a multitude of

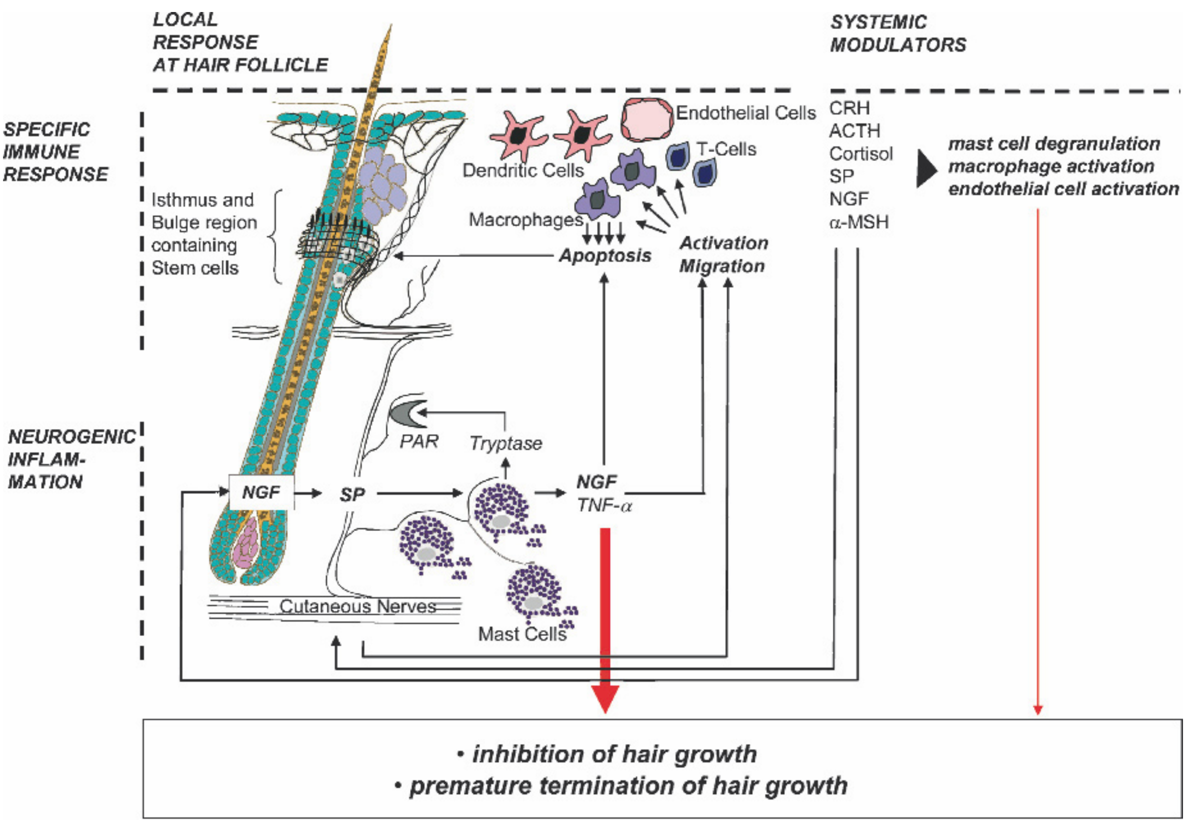


Fig. 3.4 The "neuroimmune–hair follicle axis". This schematic drawing summarizes neuroimmune interaction and its impact on hair-growth regulation as an example of the interdependence of growth factor signals on neurogenic inflammatory signals and specific immune responses. (*ACTH* Adrenocorticotropic hormone, *α-MSH* alpha melanocyte stimulating hormone, *CRH* corticotrophin-releasing hormone, *NGF* nerve growth factor, *PAR* proteinase-activated receptor, *SP* substance P, *TNF-α* tumor necrosis factor alpha)

pro-inflammatory mediators, such as histamine, into interfollicular tissue [6, 7, 40]. Mast cell release of histamine, proteases and additional neuropeptides initiates neurogenic inflammation, a defense mechanism created to provide fast host defense against microbial and parasitic intruders [6]. Subsequent inflammatory cascades involving cytokines released by mast cells or triggered by mast cell secretagogues produce a more specific immune response [40]. This inflammatory cascade headed by SP and NGF is dependent on neuroimmune interaction and has lately been implicated as a prominent aggravating factor in the premature termination of hair growth induced by environmental stressors such as noise (Fig. 3.4) [5, 37].

It has been shown that upon acute stress exposure NGF is released into the blood, e.g., from submaxillary glands of male mice [1] and perhaps other sources, making it a likely mediator of stress. The role of NGF as a local stress-response mediator involved in neurogenic inflammation was also recently established in a mouse model for perceived psycho-emotional stress [37]. In this model, a stress-induced increase in the numbers of apoptotic cells in the HF can be antagonized by NGF neutralization [37], demonstrating an important role for NGF in stress-induced HF damage. Remarkably, serving this role, NGF triggers complex skin and HF responses to stress [37]. On the one hand, NGF can promote the outgrowth of SP-positive nerve fibers, e.g., towards mast cells, thereby building up a network that allows for increased neurogenic inflammatory responses upon exposure to stress [20, 43]. On the other hand, NGF can stimulate mast cell degranulation and the release of pro-inflammatory cytokines by itself [24]. Although the roles for Trk and p75NTR in the control of this very complex pathobiological response remain to be elucidated, these data suggest that both Trk and p75NTR antagonists may be used for preventing stress-induced skin and hair-growth abnormalities.

3.7 Neuroimmunological Interactions in Autoimmune Hair Loss

Alopecia areata (AA) is an autoimmune disorder of the HF characterized by intra- and perifollicular inflammatory cell infiltrates consisting of CD4+ and CD8+ T-lymphocytes, macrophages, and Langerhans cells that target follicular keratinocytes, melanocytes, and dermal papilla fibroblasts [23, 27, 28, 33, 44]. Aberrant expression of human leukocyte antigen (HLA) classes I and II occurs in keratinocytes of the hair bulb, leading to the autoimmune attack by CD8+ T-lymphocytes, followed by the development of inflammatory cell infiltration in and around the HFs [17, 18, 21].

Human HFs affected by AA are innervated by SP-immunoreactive nerve fibers, which may modulate the perifollicular immune response [22, 23]. Interestingly in this context, a link between AA and stress has been described in humans [19, 29]. To better understand the role of SP as an immunomodulatory neuropeptide in AA, we studied its expression and effects on immune cells in the C3H/HeJ mouse model of AA [45]. Our data reveal that the number of nerve fibers containing SP strongly depends on the disease stage: during the early phase of AA development, the number of SP-immunoreactive nerve fibers in skin increased, compared to non-affected mice [45]. However, during the advanced stage of AA, the number of SP-immunoreactive nerves and SP protein levels in skin decreased, whereas the expression of the SP-degrading enzyme neutral endopeptidase increased, compared to control skin [45]. In AA, the SP-binding neurokinin-1 receptor (NK-1) is expressed on CD8+ lymphocytes and macrophages accumulating around affected HFs. Additional SP supply to the skin of AA-affected mice leads to a significant increase of mast cell degranulation and to accelerated HF regression (catagen), accompanied by an increase of CD8+ cells expressing granzyme B. These data suggest that SP, neutral endopeptidase and NK-1 receptor serve as important regulators in the molecular signaling network modulating the inflammatory response in autoimmune hair loss.

Numerous indications suggest that neurotrophins also play an important role in the pathogenesis of autoimmune diseases [2, 3]. We have recently shown that in the C3H/HeJ mouse model for AA steady-state levels of NGF, BDNF, NT-3 and NT-4 proteins determined by enzyme-linked immunosorbent assay (ELISA) remain similar to that seen in control unaffected skin [8]. These data are consistent with previous reports showing high levels of neurotrophins in other autoimmune disorders [2, 3]. In C3H mouse back skin, anagen HFs not affected by AA showed moderate expression of NGF, the absence of BDNF and co-expression of Trk and p75NTR in the outer root sheath. In the AA-affected anagen HFs, the levels of NGF and BDNF were elevated in the outer and inner root sheaths, respectively, and all Trk receptors were downregulated in the outer root sheath. In contrast, the apoptotic receptor p75NTR was upregulated in the outer root sheath and was ectopically expressed in the dermal papilla.

We also showed that neurotrophins were strongly expressed in macrophages in inflammatory cell infiltrates around the HFs. In the AA-affected skin, CD4+ cells expressed TrkB and TrkC. In the inflammatory infiltrates, numerous macrophages identified by MOMA-2 immunoreactivity co-expressed TrkB, while dermal dendritic NLDC145-immunoreactive cells were also p75NTR-positive. Double immunolabeling showed that CD8+

cells in the inflammatory infiltrates also expressed p75NTR, implicating the involvement of neurotrophins in the control of apoptosis in CD8+ lymphocytes [8]. While the significance of these observations remains to be further determined, they support the general idea that neurotrophins may modulate AA development by targeting cutaneous nerves, immune cells, and HF keratinocytes.

3.8 Experimental Techniques

Neuroimmunology of the HF is best studied in animal models, since the detection, display and, most importantly, the statistical analysis of data from nerve fibers and neuronal mediators in concert with immune cells all require the analysis of complex tissue interactions and special acquisition techniques [42]. The respective signaling molecules are small and rapidly digested after tissue dissection, demanding pericardial perfusion with a fixative such as paraformaldehyde for optimal detection. The animal model also allows us to follow neuronal plasticity through analysis of defined time points during an experimental setting [42], a task difficult to achieve in humans.

In the animal model it is possible to eliminate or enhance specific neuroimmune interaction pathways or signaling cascades to probe their functional relevance and possible therapeutic value. Neurotrophins, for example, can be knocked out or overexpressed transgenically [13]. Experiments along this line led to the pathophysiological insights into hair cycle control discussed above. Other models involve established hair disease models such as that for AA. In this model SP has been shown to play an initiating role in the inflammatory cascade leading to selective inflammatory destruction of anagen HFs (see above).

Surgical or pharmacological denervation or inhibition of neuronal mediator signaling has also been proven as a useful measure to analyze the impact of neuroimmune interactions on hair growth. In denervated skin for example hair growth appears to terminate, while increased hair growth could be observed in hyperinnervated skin, demonstrating the dependence of hair growth regulation on growth factors derived from nerve fibers [31, 39]. Furthermore, organ culture experiments employing denervated skin exposed to selective neuropeptides demonstrate that SP acts as a hair growth stimulator through direct growth factor capacities [31, 39]. This latter organ culture experiment demonstrates that the study of neuroimmune interactions and their effect on hair growth in vitro is suitable for evaluating the direct actions of neuroimmune mediators on hair growth. However, it is at the same time limited to the analysis of individual HF cell populations and their response, but does not supply insight into the net effect of local and additional systemic signaling by the respective molecules. For example, culture models have shown that, like SP, CGRP and vasoactive intestinal peptide (VIP) can also promote keratinocyte proliferation in mice and humans [31, 38]. Neurotransmitters such as noradrenaline (norepinephrine) and neurotrophins have also been shown to promote keratinocyte proliferation in culture. However, in vivo hair growth experiments show that neuropeptides and neurotrophins do not necessarily enhance hair growth through their promotion of keratinocyte proliferation [8, 13, 31]. Indeed, they may have quite the opposite effect, either by interacting with receptors that aren't necessarily expressed on cultured cells but are found in crucial locations on the growing HF, or through the induction of deleterious perifollicular inflammation, which then overrides any direct growth-promoting effects on HF cells.

On occasion the analysis of cell-to-cell interactions may also be elucidating for hair research and the pharmacological targeting of hair growth mechanisms. Nerve fibers for example can be co-cultivated with mast cells, and experiments have shown that mast cell degranulation is positively enhanced in the presence of SP-positive nerve fibers [48].

3.9 Clinical Relevance

Most of our knowledge on the neuroimmune regulation of hair growth has been gained in experiments using animal models, especially when it comes to pharmacologic or other therapeutic interventions. In the mouse, NK-1 antagonists, NGF-neutralizing antibodies and surprisingly minoxidil [4, 5, 37] are all capable of counteracting stress-induced deleterious neurogenic inflammation. NK-1 antagonists and minoxidil thereby appear to be especially promising compounds to be used in the pharmacotherapy of hair loss associated with neurogenic inflammation, since they have long been approved as therapeutic agents in humans. However, if results like those obtained in animal models can be reproduced in humans, they remain speculative despite promising in vitro data [39, 41]. Our knowledge to date therefore primarily serves to inform and enlighten patients with unwanted hair loss, especially under stress and in the inflammatory context – patients who are often frustrated by the narrow treatment options available to them and the small number of medical personnel who can provide expert knowledge. It remains a challenging research task for future efforts to prove the effectiveness of pharmaceuticals that target neuroimmune interactions and to test further target compounds, such as specific CGRP-

receptor antagonists, mast cell stabilizers and the depletion of nerve fibers, e.g., by capsaicin.

3.10 Outlook – Future Developments

We have learned of many of the neuroimmune interaction pathways that affect hair growth; however, this research has resulted in few clinical approaches to master unwanted hair loss, for example. This means that further research and testing of highly specific neurotransmitter, neuropeptide and neurotrophin agonists and antagonists are required. Minoxidil, for example, is one of the few hair growth remedies on the market, although we understand little about its function. One relevant mechanism through which it may be effective is the inhibition of neurogenic inflammation, as has been shown in the mouse model [4, 39]. However, clinical follow-up studies to confirm this effect in the human have yet to be performed.

Summary for the Clinician

The hair follicle (HF) is densely innervated and possesses a unique array of immune cell populations. This provides each HF with neuroimmune interaction pathways that adapt local hair-growth regulatory pathways to systemic requirements, for example in temperature regulation or protection from injury. It also explains why the HF so often acts as a messenger for systemic disease. Denser hair growth, for example, can be expected after neuronal activation through injury, while stimulation of neurogenic inflammation, for example through stress, can terminate hair growth. Knowledge of these interaction pathways does not yet provide us with many clinically approved treatment options, however imparting careful and sound information gives great relief to many patients, who have difficulty in understanding their hair loss and are frightened that they have lost their hair for ever.

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Chapter 4

Biology of Hair Follicle Pigmentation

Desmond J. Tobin

4

Synonyms
hair color, melanin production, melanogenesis

Key Features

- The hair follicle and epidermal pigmentary units are broadly distinct and can be distinguished principally on the basis of the former's stringent coupling to the hair growth cycle compared to the latter's continuous melanogenesis.
- Melanin synthesis and its transfer from melanocyte to hair bulb keratinocytes both depend on the availability of melanin precursors and are regulated by cutaneous signal transduction pathways that: (1) are both dependent and independent of receptors, (2) act through auto-, para- or intracrine mechanisms, and (3) can be modified by hormonal signals.
- Follicular melanocytes appear to be more sensitive than epidermal melanocytes to aging influences, as indicated by dramatic hair graying/canities. This is likely to reflect differences in the epidermal and follicular microenvironments.
- Skin and hair color contribute significantly to our overall visual appearance and to social/sexual communication; thus disorders of follicular pigmentation may cause psychological trauma.
- Hair pigment may also contribute to rapid excretion of heavy metals, chemicals, and toxins from the body by their selective binding to melanin.
- The availability of cell culture methodology for isolated hair follicle melanocytes and for intact anagen hair follicle organ culture, as well as improved technologies for follicular delivery in vivo should provide important research tools for elucidating the regulatory mechanisms of hair follicle pigmentation.

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4.1 Introduction

As social beings we communicate significantly via our physical appearance. Skin and hair color contribute disproportionately to this overall visual demeanor. The main contributor to this phenotypic palette is a class of mixed indole-rich compounds called *melanins* formed within unique cytoplasmic organelles called *melanosomes* produced within the *melanocyte* via a complex, phylogenetically ancient, biochemical pathway called *melanogenesis.*

While hair growth and pigmentation facilitated evolutionary success in non-human mammals (i.e., via thermal insulation, camouflage, social and sexual communication, and sensory perception) these traits do not appear to have been critical for survival in humans. Why humans should be unique among primates in exhibiting pigmented scalp hair that is very thick, long, and pigmented remains unclear, but it is likely to reflect particular evolutionary selective pressures present during the early stages of human evolution. One possible explanation may pertain to human evolution by seacoasts and riverbanks where fish was a dominant part of our early diet. As many fish species concentrate heavy metals it would have been important to develop strategies to prevent the build-up of toxic metals. This could be readily achieved by their selective binding to melanin in a rapidly growing and melanized tissue. The hair follicle is a highly proliferative tissue in which melanin-accepting bulbar keratinocytes form the pigmented hair shaft. In this way the trapping of toxins (including heavy metals) within long, deeply melanized, scalp hair fibers would limit their access to the living tissue of the highly vascularized scalp. Furthermore, our relative nakedness draws much attention to our facial and scalp hair. These modifications may have been critical for the development of optimal communication strategies.

Deep brown-black hair is the norm for over 90% of the world's human population. Indeed, it may appear somewhat paradoxical that black scalp hair also predominates in primates (including humans) living in tropical climes, where the thermal insulating properties of melanin (via trapping of radiant heat) appears to be misplaced. A possible explanation may be protection against sunstroke afforded by deep skin and hair pigmentation, as well as the contribution of melanin's very efficient and fast exchange of ion transport and efflux to adequate salt balance [88]. So what about the remaining 5%–10% of the world's population (mostly originating in northern Europe) who have emerged with a bewildering array of hair colors that range from white blonde, yellow blonde, auburn to red and all shades in between? Recent advances in molecular genetics have started to yield clues to explain the basis of this dramatic diversity of human cutaneous pigmentation whereby these phenotypes appear to be linked to the degree of variability (i.e., polymorphism) in the melanocortin-1 receptor (MC1R) gene [51]. This receptor is activated through binding of the pro-melanogenic peptides α-melanocyte stimulating hormone (α-MSH) and adrenocorticotropin hormone (ACTH). For example, most northern Europeans with red hair are homozygotes or compound heterozygotes for a limited number of MC1R mutations [50]. Natural selection pressures may have restrained mutation of this gene in the hot, humid and sunny tropics, thereby ensuring dark hair and skin. These pressures may have been less critical as humans migrated from Africa to less sunny, less humid, colder northern climes, such that the "brake" on gene mutation was lifted, resulting in the emergence of functionally relevant mutations in the MC1R gene. Indeed, more recent data suggest that variations in the MC1R are common in non-African populations [51]. Sadly, regardless of our original natural hair color, the follicular melanin unit appears to have an intrinsic "biologic clock," and canities is the inevitable harbinger of disappearing youth.

This chapter aims to discuss our current thinking on several aspects of follicular pigmentation biology in humans. Much of this knowledge derives from the intensive study of murine coat color. This species exhibits a high level of coat color mutations, and correlates of these continue to be discovered in humans. There is a caveat here as recent research highlights several differences in the regulation of melanogenesis between mice and humans. I will begin with an assessment of how the follicular pigmentary unit is structurally configured during development, before focusing on the hair-cycle-specific influences on the follicular melanocytes that do not impact on melanocytes in the epidermis. This will be followed by close examination of the regulation of melanin synthesis and its transfer from melanocyte to hair bulb keratinocytes, which involves cutaneous signal transduction pathways that are both dependent and independent of receptors, that act through auto-, para- or intracrine mechanisms, and that can be modified by hormonal signals. From there we will examine our current understanding of the mechanisms underlying follicular

melanocyte aging that result in hair graying/canities, as well as the pathologic basis of selected hair pigmentation disorders [80], before concluding with a brief assessment of how new experimental techniques may facilitate further advances in hair pigmentation sciences. A glossary of key terms is provided in Table 4.1, page 70.

4.2 History

It was not until the seventeenth century that a scientific approach to the study of pigmentation was reported by Italian anatomist Malphigi. From then, fast forward to 1950s USA where the rigors of cellular and molecular analyses were applied to the study of pigmentation of the epidermis. Pivotal descriptions of the "epidermal melanin unit" and the dissection of elements of the melanin biosynthetic pathway (melanogenesis) followed in the 1950s by Fitzpatrick and Breathnach [17], and by Lerner and Fitzpatrick [37]. The study of follicular pigmentation in particular was significantly advanced by an exceptional report by Fitzpatrick, Brunet and Kukita [18] in 1958 entitled The nature of hair pigment, which featured prominently in Montagna and Ellis' seminal book *The Biology of Hair Growth*.

4.3 Structure and Function/ Pathophysiology/Developments

4.3.1 Origin and Development of the Hair Follicle Pigmentary Unit

Melanocytes of both the epidermal melanin unit and the follicular pigmentary unit derive from melanoblasts that migrate from the neural crest to the skin. Commitment and differentiation of cells of the melanocytic lineage in the neural crest are determined by several factors including, amongst others, microphthalmia-associated transcription factor (MITF), SOX10, Pax3, KIT, fibroblast growth factor-2, and endothelin 3 (Fig. 4.1) [15]. Melanoblasts migrate out of the neural crest along ste-

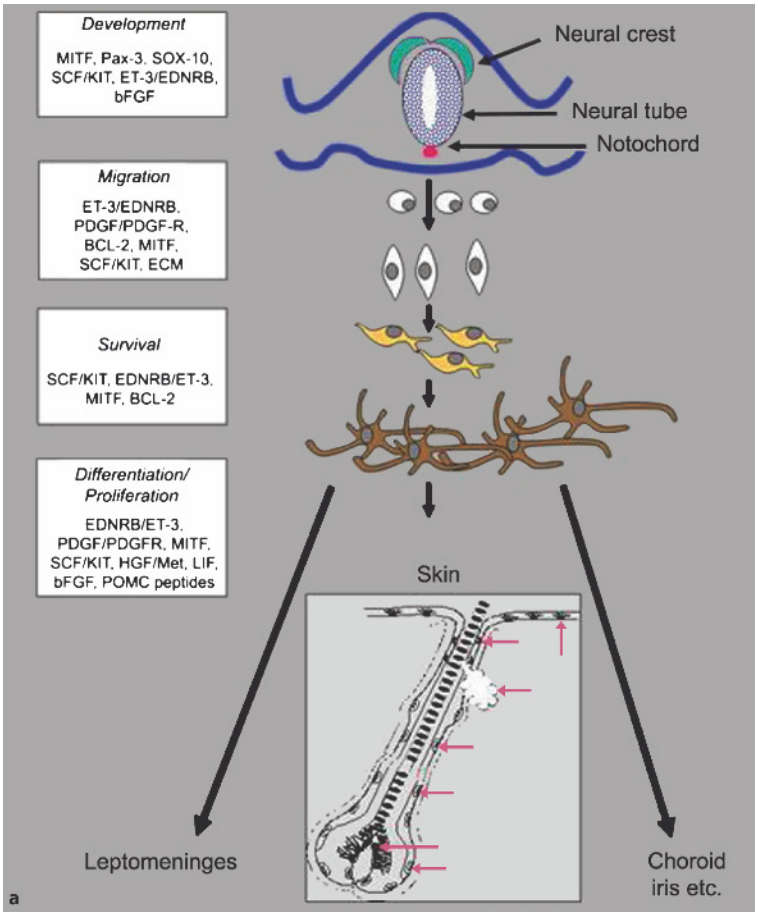


Fig. 4.1 **a** Melanocyte development. Melanocytes migrate from the neural crest to the skin and hair follicle along stereotyped routes and are spatiotemporally influenced by a range of developmental and differentiation cues. [*BCL-2* B-cell CLL/lymphoma 2, *bFGF* basic fibroblast growth factor, *ECM* extracellular matrix, *EDNRB* endothelin B receptor, *ET-3* endothelin-3, *HGF* hepatocyte growth factor, *KIT* stem cell factor receptor, *LIF* leukemia inhibitory factor, *Met* HGF receptor, *MITF* microphthalmia-associated transcription factor, *Pax3* paired box gene 3, *PDGF(R)* platelet-derived growth factor (receptor), *POMC* pro-opiomelanocortin, *SCF* stem cell factor, *SOX10* SRY-box containing gene 10.] Adapted from Tobin & Bystryn [72]

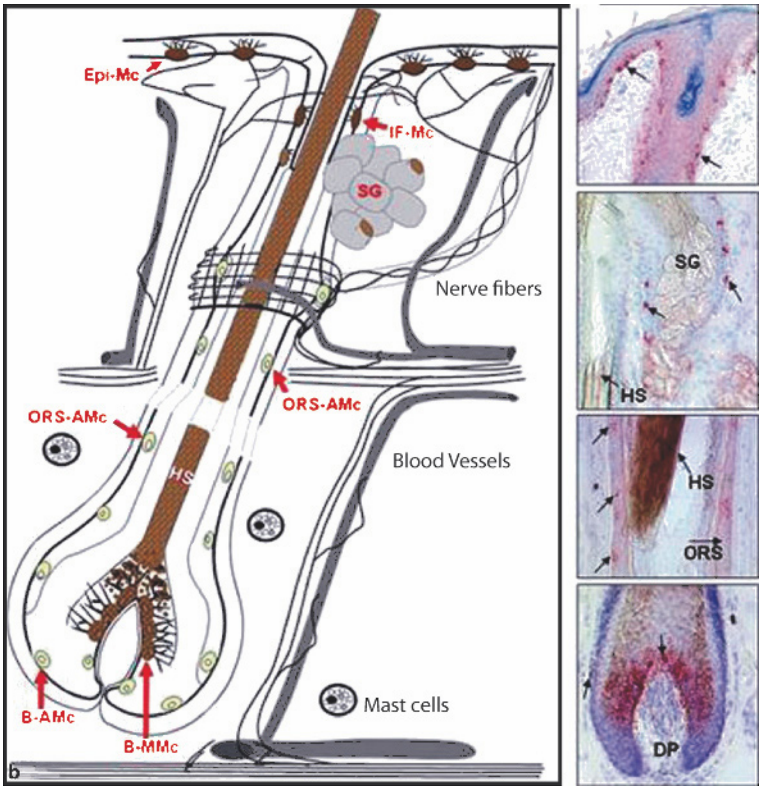


Fig. 4.1 (*continued*) **b** Schematic and immunohistologic representations of the distribution of melanocyte subpopulations in different regions of the human anagen scalp hair follicle. Melanocytes in frozen scalp sections were detected using the antibody NKI/beteb to gp100. (*B-AMc* Bulbar amelanotic melanocyte, *B-MMc* bulbar melanogenic melanocyte, *DP* dermal papilla, *Epi-Mc* epidermal melanocyte, *HS* hair shaft, *IF* infundibulum, *ORS-AMc* outer root sheath amelanogenic melanocyte, *SG* sebaceous gland.) Adapted from Tobin [69]

reotypic routes to enter the dermis of the skin. Melanogenesis occurs very early during human embryologic development and melanocytes can be detected in human skin as early as 7 weeks of gestation [24] with pigment synthesis some 5 months before birth. Indeed, some migrating melanoblasts/melanocytes are already melanogenically active in the murine dermis before arriving at the epidermis [48] and before hair follicle development commences [24].

Some melanoblasts proliferate and differentiate into melanocytes while residing in the epidermis, while others and their progeny, so-called *transit-amplifying* melanocytes, leave the epidermis to distribute in the developing hair follicles as dopa-positive and dopa-negative cells in the hair follicle and its associated sebaceous gland. Melanogenic melanocytes and melanoblasts can be detected at all stages of hair morphogenesis, from the germ stage (Stage 2) onwards [48]. KIT-positive melanoblasts migrate into the hair follicle epithelium, which is a source of stem cell factor (SCF), and when differentiated target the hair bulb when it expresses SCF [48]. Once hair fiber formation commences, melanocytes concentrate at the basal lamina around the apex of the follicular dermal papilla, while KIT-negative amelanotic melanocytes/melanoblasts invade the outer root sheath and bulge region in the fully developed hair follicle [48]. Analysis of mutations that effect differentiation, proliferation, and migration of melanocyte precursors in mice has helped to clarify the events involved in the development of melanocyte compartments within the skin and hair follicle. Of the more than 90 loci shown to affect hair color in the mouse [42], mutations in the receptor tyrosine kinase KIT and its cognate ligand SCF, and endothelin 3 and its receptor Ednrb have been most informative. Mutant homozygotes exhibit an almost complete lack of hair pigmentation. The importance of the KIT–SCF signaling pair is evident from the ability of a KIT-blocking antibody to induce apoptosis in murine follicular melanocytes [29].

4.3.2 Comparative Biology of Epidermal and Hair Follicle Melanocytes

The relative independence of the epidermal– and follicular–melanin units can be appreciated by the co-expression of white hair and black skin in aging Africans and conversely raven hair in white-skinned Europeans. This is further supported clinically, by the selective/preferential targeting of epidermal but not follicular melanocytes in most cases of vitiligo, while follicular melanocytes alone are damaged by immune-mediated pathology in acute alopecia areata [70, 73]. In the fully developed anagen human scalp hair, follicle

melanocytes can be detected in distinct anatomic compartments with region-specific differentiation status (Figs. 4.1, 4.2). In the mature hair follicle, melanotic melanocytes positive for 3,4-dihydroxy phenylalanine (dopa) are readily detectable in the basal layer of the infundibulum and around the upper dermal papilla; moderately differentiated melanocytes may also be detected in the basal layer of the sebaceous gland. However, the hair bulb is the only site of pigment production for the hair shaft (Figs. 4.1, 4.2a,b), and contains both highly melanogenic melanocytes and a minor subpopulation of poorly differentiated melanocytes [69, 74]. Melanogenically active melanocytes are however restricted to the upper hair bulb matrix, just below the precortical keratinocytes, a location that facilitates the transfer of melanin to the hair shaft cortex, less so to the medulla, and very rarely the hair cuticle (Figs. 4.1, 4.2).

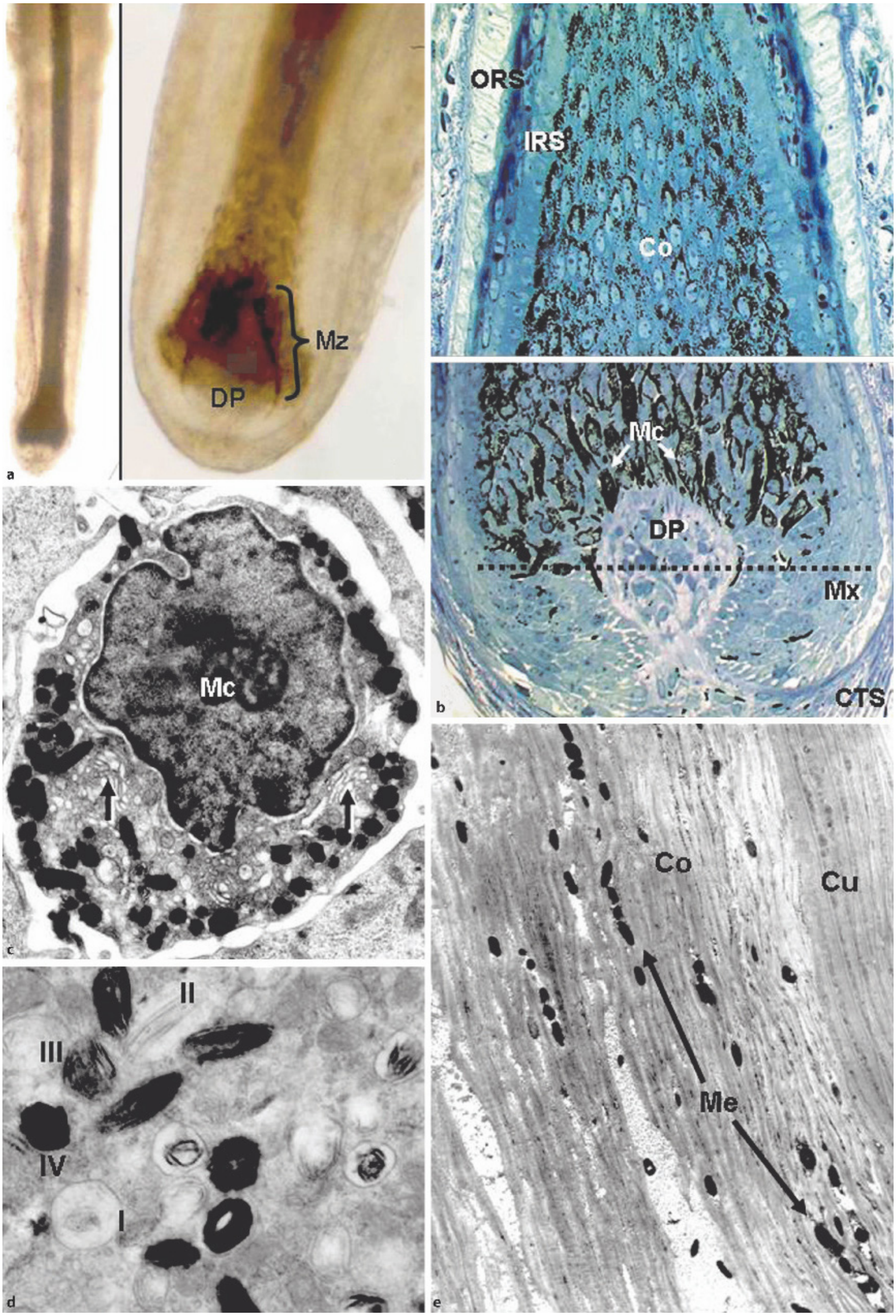
The presence of immature melanocytes (melanoblasts) in fully developed adult anagen hair follicles has been confirmed in situ and in vitro [26, 69]. Dopa-negative amelanotic melanocytes appear in the mid-to-lower outer root sheath, but also in the periphery of the bulb and the most proximal matrix. All the dopa-positive cells, and also some dopa-negative melanocytes of the mid outer root sheath contain (pre)melanosomes (i.e., gp100-positive) [26]. Although amelanotic hair follicle melanocytes lack dopa-oxidase activity, low levels of the tyrosinase protein itself may be detected in some cells, as well as KIT and Bcl-2. These melanocytes do not express the melanogenic enzymes tyrosinase-related protein-1 (TRP1) and TRP2 (dopachrome tautomerase, DCT) [26]. The role of these amelanotic melanocytes in hair pigmentation is unclear, although it has been speculated that these cells represent a pool of "transient" melanocytes that migrate from precursor melanocyte stores in the upper outer root sheath [57, 79, 82]. This melanocyte pool may be targeted in an attempt to intervene biotechnologically in impaired hair pigmentation. This multi-functionality of follicular melanocyte subpopulations is further attested by their complex responses to chemotherapy [59, 79].

Recent immunologic data have shown that the "follicular–melanin unit" resides in the immune-privileged proximal anagen hair bulb (c.f. [65]). Melanocytes of the follicular–melanin unit are larger, more dendritic, have more extensive Golgi and rough endoplasmic reticulum (ER), and produce larger melanosomes compared to melanocytes in the epidermal–melanin unit (c.f. [72]). While melanin produced by the latter degrades almost completely in the differentiating layers of the epidermis, eumelanin granules transferred into hair cortical keratinocytes remain minimally digested; hence, the similarly pigmented proximal and distal ends of a typical hair shaft (c.f. [72]). By far the most striking difference between the epidermal– and follicular–melanin units, and one with significant implications for the regulation of hair pigmentation, is the observation that the activity of the hair bulb melanocyte is under tight cyclical control and that melanogenesis is coupled to the hair growth cycle (c.f. [56]). Epidermal melanogenesis, by contrast, appears to be continuous [44], though this constitutive activity can be stimulated further, e.g., after exposure to UV radiation.

4.3.3 The Fate of Hair Follicle Melanocytes During the Hair Growth Cycle

Active pigmentation occurs only during the hair growth phase (anagen) (Fig. 4.3a), which in human scalp hair can be very long (up to 8 years or more) [65]. This extended anagen of human scalp hair, together with its mosaic pattern of hair growth, hinders systematic analysis of melanocyte dynamics during the human hair cycle. However, the C57BL/6 mouse has proven to be a very useful model for human hair pigmentation, given their short anagen (15–17 days), synchronous hair growth pattern, restriction of melanogenically active truncal melanocytes to the hair follicles, exclusively eumelanin production, and the similar linkage of murine melanogenesis with anagen (Fig. 4.3b) [57].

The relatively quiescent telogen hair germ contains all cell precursors needed to reconstitute a fully developed anagen VI hair follicle. Tracking melanocyte subpopulations during the hair cycle has exploited the expression of melanogenesis-related proteins (or their mRNA) including tyrosinase, and related proteins TRP1 and DCT, in addition to KIT and the proliferation marker Ki67. In this way the extent of melanocyte differentiation can be followed both temporally during the hair cycle and physically throughout the different hair follicle anatomic compartments. During telogen C57BL/6 murine skin does not contain tyrosinase (mRNA or protein), TRP1 protein or melanin and has only very low levels of tyrosine hydroxylase activity [55]. Some melanocytes/melanoblasts from the telogen secondary germ are immunohistochemically positive for DCT, and, of these, a subpopulation also expresses KIT [9]. These melanocytes are mitotically quiescent, as assessed by Ki67 immunostaining. However, during the first 1 or 2 days of anagen induction some cells begin to express tyrosinase message and protein becomes barely detectable. During this time (i.e., anagen I) TRP1, and the tyrosine hydroxylase and dopa oxidase activities of tyrosinase remain undetectable enzymatically. However, some DCT-positive melanocytes begin to express TRP1 at this stage, especially melanocytes located close to the forming hair bulb, while melanocytes residing in the upper outer root sheath (site of the presumptive germ cell reservoir) remain TRP1 negative. A second subpopula-


Mz
DP
a
ORS
IRS
Co
Mc
DP
Mx
CTS
b
Mc
c
II
III
IV
I
d
Co
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Me
e

◀ **Fig. 4.2a–e** Anatomy, histology and ultrastructure of the hair follicle pigmentary unit. **a** Intact pigmented anagen hair follicles isolated from normal human scalp tissue. Note the location of the intensely pigmented melanogenic zone (*Mz*) around the dermal papilla (*DP*). **b** Longitudinal section of human anagen scalp hair follicle. Note that melanocytes remain intensely pigmented and transfer melanin only to the precortical keratinocytes. (*Co* Cortex, *CTS* connective tissue sheath, *DP* dermal papilla, *IRS* inner root sheath, *Mx* matrix, *ORS* outer root sheath, *dash line* Auber's Line.) **c** Transmission electron micrograph of a hair bulb melanocyte in a human scalp anagen hair follicle. Note that cell contains large numbers of maturing and fully mature melanosomes and well-developed Golgi apparatus (*arrow*). **d** Transmission electron micrograph of part of a hair bulb melanocyte in a human scalp anagen hair follicle. Note the presence of early pre-melanosomes (*I* and *II*), maturing melanosomes (*III*) and fully mature ellipsoidal eumelanosomes (*VI*). **e** Transmission electron micrograph of a longitudinally sectioned hair shaft cortex revealing the distribution of melanin granules (*Me*) between cortical cells (*Co*) but not in the cuticle (*Cu*). Adapted from Tobin [70]

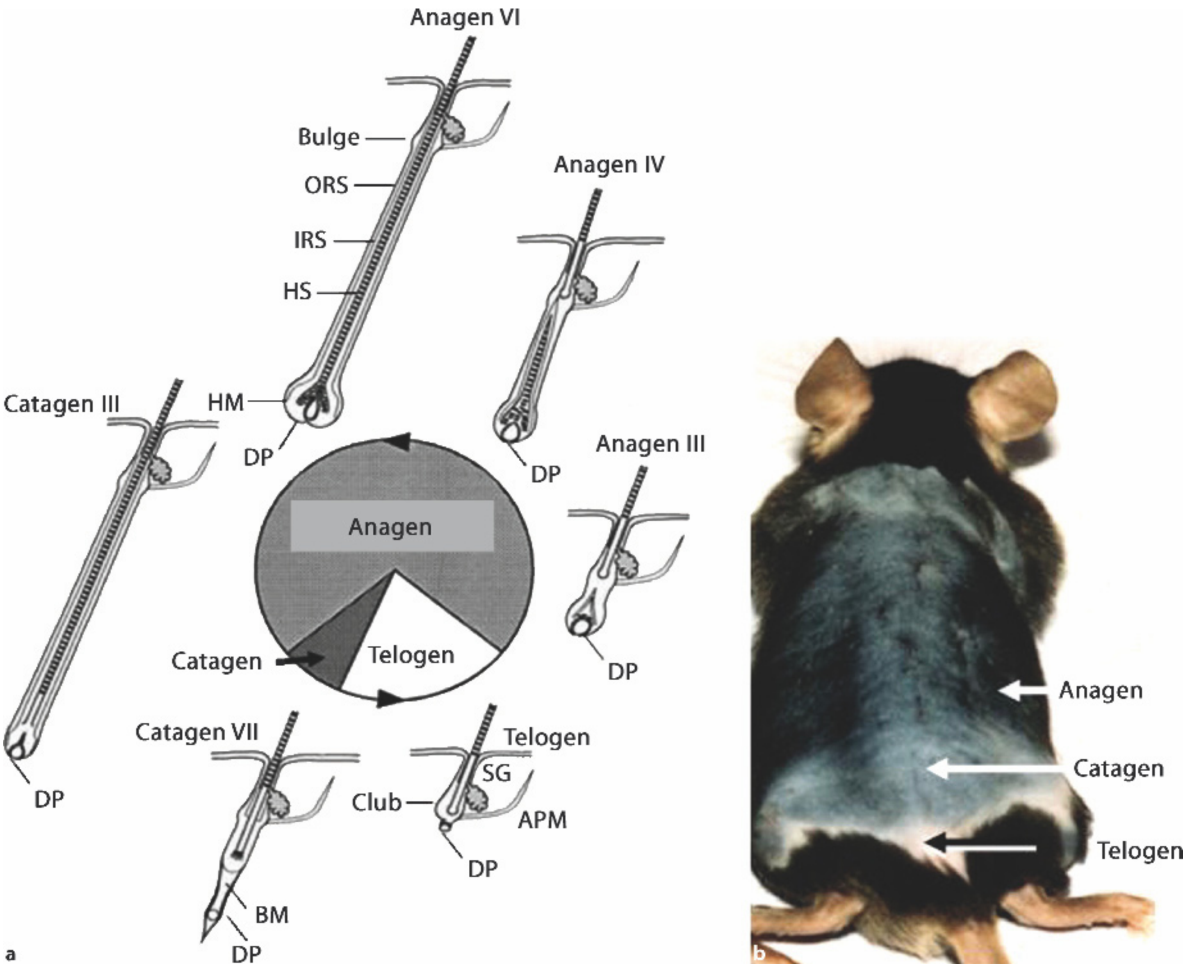


Fig. 4.3 **a** Schematic representation of the hair growth cycle. (APM Arrector pili muscle, BM basement membrane, DP dermal papilla, *HM* hair matrix, *HS* hair shaft, *IRS* inner root sheath, *ORS* outer root sheath, *SG* sebaceous gland.) Adapted from Tobin & Paus [75]. **b** Depilated back of C57bl/6 mouse showing regions of the pelage in synchronous anagen (black), catagen (gray) and telogen (pale pink) stages of the hair growth cycle

tion, which expresses TRP1 or DCT together with KIT, begins to show proliferative activity.

The follicular papilla of early anagen hair follicles can pool high concentrations of l-phenylalanine, a potential requirement for the supply of l-tyrosine for melanogenesis [54]. Conditions that support the production of high amounts of l-tyrosine from l-phenylalanine include high levels of $6BH_4$, GTP-cyclohydrolase 1, and phenylalanine hydroxylase (PAH). All three are high from earliest anagen through to anagen III, after which the activities of all three drop significantly and remain low until the next telogen. Low $6BH_4$ levels may be necessary during pigment production to prevent its allosteric inhibition of tyrosinase. Just prior to this early anagen-associated drop (i.e., anagen II), tyrosinase message, protein, and activity all begin to increase rapidly to peak at early anagen VI (full anagen). Similarly, low thioredoxin reductase activities during anagen II and III promote more oxidizing conditions necessary for the initiation of melanogenesis. The gradual increase of thioredoxin reductase during anagen V to catagen could neutralize reactive oxygen species (ROS) produced by melanogenesis (c.f. [54]).

The anagen-associated stimulation of undifferentiated telogen melanocytes/melanoblasts predates the melanogenic stimulus delivered during anagen III, which in turn is followed by active melanogenesis and the subsequent transfer of mature melanosomes into keratinocytes of the precortical matrix. Melanocytes in the S-phase of the cell cycle have been reported as early as anagen II and significant proliferation is clearly apparent in anagen III [66]. Bulbar melanocytes during the transition from anagen III to anagen VI increase in number, in dendricity, develop more Golgi and rough endoplasmic reticulum, increase the size/number of their melanosomes, and begin to transfer mature melanosomes to precortical keratinocytes.

By anagen IV, when the hair pigmentary unit becomes fully functional with respect to melanin synthesis, melanocytes are distributed into discrete locations throughout the hair follicle (Figs. 4.1, 4.2). Melanocytes localized to the murine HF bulge (site of presumptive reservoir) express only DCT, lacking TRP1, KIT, and Ki67 immunoreactivities. Melanocytes located in the elongating outer root sheath express DCT and KIT and in some cases are also positive for the proliferation marker Ki67, but express little TRP1 and no tyrosinase [9]. Only melanocytes distributing to the hair follicle melanogenic zone, i.e., the hair bulb matrix above the DP, express TRP1, DCT, tyrosinase, KIT, and also Ki67 in the majority of melanocytes. DCT protein is undetectable in melanogenic melanocytes of the human anagen hair bulb [12], highlighting an important species-specific difference with mice. Melanocyte proliferation ceases by anagen VI (full anagen). Both the activity and concentration of tyrosinase remain constant during mid to late anagen VI, and decrease rapidly during the anagen VI to catagen transition phase, to become undetectable or very low in catagen [57]. The expression of other melanogenesis-related proteins follows a similar pattern. This physiologic decrease in follicular melanogenesis may reflect two possible mechanisms for termination of melanogenesis; namely, exhaustion of an active signaling system that stimulates melanogenesis, and/or the production of inhibitors of melanocyte activity [46, 61].

Even before catagen-associated structural changes are apparent in the hair bulb, the earliest signs of imminent hair follicle regression include the retraction of melanocyte dendrites and the attenuation of melanogenesis during late anagen VI [79]. Limited keratinocyte proliferation continues for a while, so the most proximal telogen hair shaft remains unpigmented – the functional relevance of which remains enigmatic. One can detect a dramatic and rapid drop in the levels of active tyrosinase beginning during late anagen VI itself, while DCT activity exhibits moderate reductions from mid to late anagen VI and is lowest during catagen. Pterin synthesis and PAH activities are low during catagen, while thioredoxin reductase levels remain elevated to provide a reducing environment. This combination decreases l-tyrosine supply and so generates conditions unfavorable for active melanogenesis [54].

A long enduring enigma of both hair follicle and pigment biology concerns the fate of the hair bulb melanocytes when they become undetectable during catagen. Where do these melanocytes go during catagen and telogen? Where do they originate from when follicular melanogenesis is resumed during the next anagen phase? [79]. Until very recently, the dominant view was that the hair bulb melanocyte system is a self-perpetuating arrangement, whereby melanocytes involved in the pigmentation of one hair generation are also involved in the pigmentation of the next [66] via multiple cycles of de-differentiation followed by re-differentiation. While there is evidence of some plasticity in the hair follicle pigmentary unit, the level invoked by the self-perpetuating theory would imply a degree of plasticity not seen in most non-malignant cell systems. Moreover, fully differentiated bulbar melanocytes would also need to survive/avoid the extensive apoptosis-driven regression of the hair bulb [39] by actively suppressing apoptosis.

Our current view suggests that many of the so-called re-differentiating melanocytes in early anagen correspond to newly recruited immature melanocytes derived from a melanocyte reservoir [43, 79] and are not reactivated from pre-existing hair bulb melanocytes that were melanogenically active during the previous anagen phase. This is supported by the observation of a population of immature DCT-positive melanocytes unaffected by blocking anti-KIT antibody in the murine bulge [9].

These melanocyte "stem" cells are located at the base of the permanent part of the hair follicle and are immature, slow cycling, self-maintaining and are fully competent to regenerate progeny at early anagen [43]. Moreover, these hair follicle melanocyte stem cells appear to have the capacity to enter vacant niches, including (via migration to) the epidermis. It is possible, however, that some "new generation" melanogenically active melanocytes derive from a population of catagen-surviving melanocytes. Indeed, low numbers of apparently dendritic melanocytes can be detectable in the retreating epithelial strand of catagen hair follicles undergoing active resorption via apoptosis [11]. In any event at least a proportion of the highly melanotic (possibly terminally differentiated melanocytes) hair bulb melanocytes do not survive catagen [75]. Deletion of individual mela-

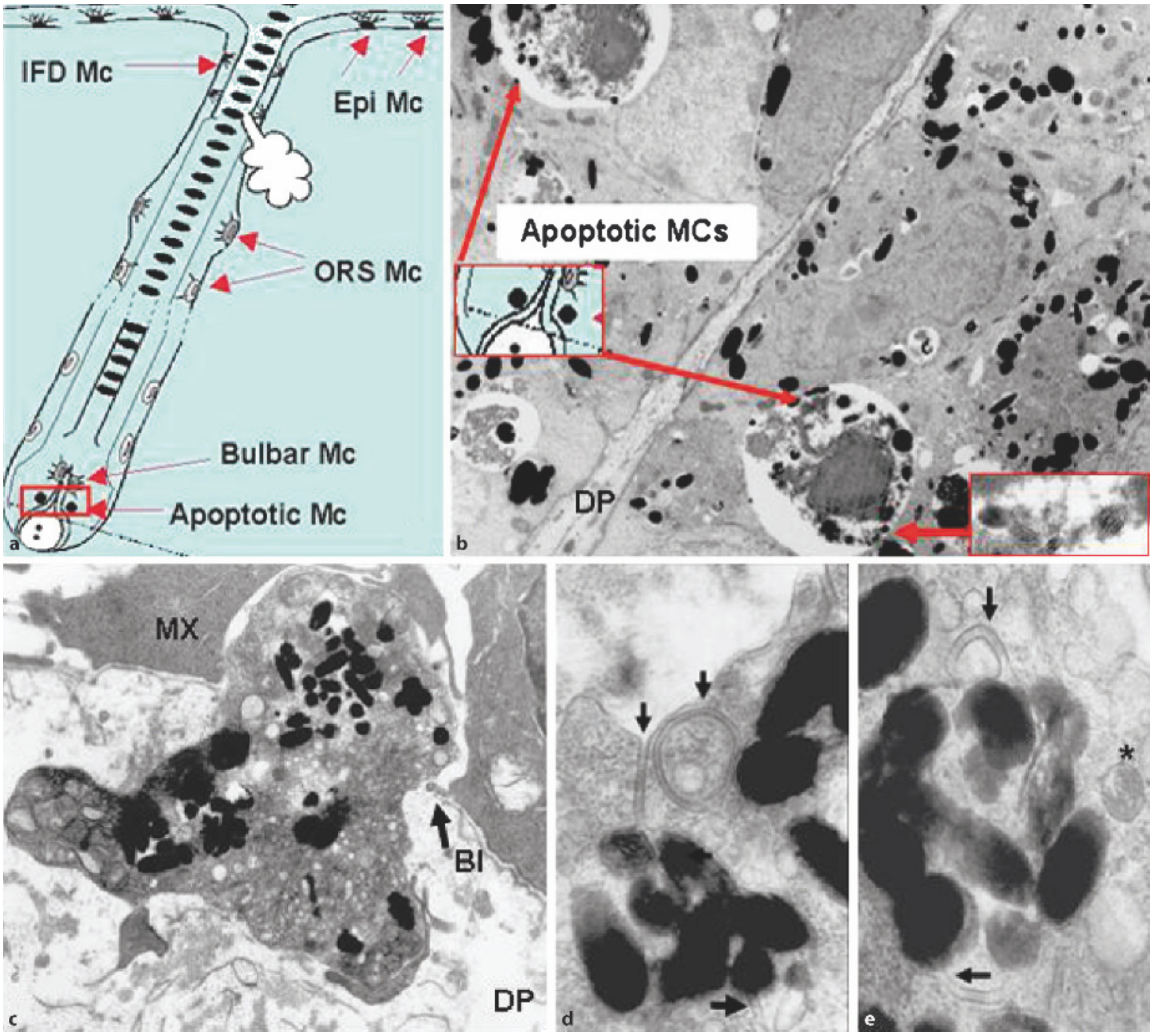


Fig. 4.4 **a** Schematic representation of an early catagen hair follicle. Note loss of some bulbar melanotic melanocytes via apoptosis. (*Epi-Mc* Epidermal melanocyte, *IFN-Mc* infundibular melanocyte, *ORS Mc* outer root sheath melanocyte.) **b** Transmission electron micrograph of section of an early catagen hair bulb showing apoptosis of two melanotic melanocytes (*MCs*). *Inset*: high-power view of premelanosomes. (*DP* Dermal papilla.) **c** Transmission electron micrograph of a section of an early catagen hair bulb showing a portion of a Langerhans cell transporting melanin from the hair matrix to the follicular dermal papilla. Note rupture of the basal lamina (*arrow*). (*Bl* Basal lamina, *DP* follicular dermal papilla, *Mx* matrix.) **d** Uptake (phagocytosis/endocytosis) of melanin showing formation of a Langerhans granule at the plasma membrane. Adapted from [68, 72]. **e** Melanosomes within an endosome/lysosome showing intimate relationship between Langerhans granule (*arrow*) and melanin granules

notic melanocytes by apoptosis was confirmed using well-described ultrastructural features (Fig. 4.4a,b) and TUNEL/TRP-1 co-localization.

Some pigment formed during late anagen fails to become incorporated into the hair shaft and instead is transported to the follicular papilla, epithelial strand or connective tissue sheath of catagen hair follicles. This redistribution of follicular pigment is likely to involve phagocytosis by macrophages, Langerhans cells, and follicular papilla fibroblasts, the first two of which increase in number during hair follicle regression (Fig. 4.4c–e).

4.3.4 Regulation of Pigmentation in the Hair Follicle

Pigmentation of hair fibers is affected by numerous intrinsic factors including: hair-cycle-dependent changes, body distribution, racial and gender differences, variable hormone responsiveness, genetic defects, and age-associated change. The multi-step nature of melanosome biogenesis and melanogenesis involves several positive and negative regulators/factors including: growth factors, cytokines, hormones, neuropeptides and neurotransmitters, eicosanoids, cyclic nucleotides, nutrients, microelements, cations/anions, etc. [44]. These factors may act via autocrine, paracrine, and endocrine mechanisms, and while much of the available literature pertains to epidermal melanocytes (c.f. Slominski et al. [60]), similar regulators (except UVR) may also operate in follicular melanogenesis. Recent data, however, suggest different roles for DCT and perhaps also TRP1 in human versus murine follicular melanocytes [7, 12].

The process of melanogenesis can be divided into: (1) melanosome biogenesis (Fig. 4.2c, d) and (2) the biochemical pathway that converts phenylalanine/l-tyrosine into melanin (Fig. 4.5). Both processes are under complex genetic control, which encodes a range of enzymes, structural proteins, transcription factors, receptors, and growth factors. Melanosome structure correlates with the type of melanin produced. Melanocytes in black hair follicles contain the largest number of, and most electron-dense, melanosomes (eumelanosomes), each with a fibrillar matrix (c.f. [82]). Brown hair bulb melanocytes contain eumelanosomes that are somewhat smaller, but phenotypically similar to black hair melanosomes, while blonde hair bulbs produce weakly melanized melanosomes with often only the melanosomal matrix visible. Red hair pheomelanosomes, by contrast, contain a vesicular matrix with melanin deposited irregularly as blotches. Less is known about the events involved in the formation of the pheomelanosome that produces the red/yellow melanin, though tyrosinase activity may appear earlier in these melanosomes. Surprisingly, both eumelanogenic and pheomelanogenic melanosomes can co-exist in the same normal human melanocyte.

The constitutive color of an individual's hair is due to absolute tyrosinase activities, rather than levels of tyrosinase protein expression. Thus, tyrosinase regulation is critical, being controlled not only by the supply of l-tyrosine but also by the stability/activity of tyrosinase and

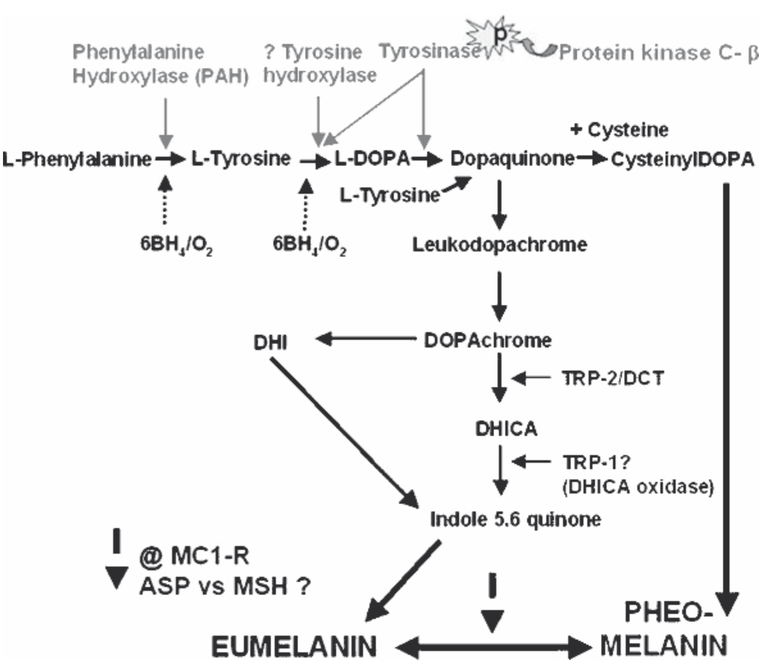


Fig. 4.5 Biosynthesis of melanins. There is some debate about some of the finer details of this pathway, especially whether the enzyme tyrosine hydroxylase (in addition to tyrosinase) can convert l-tyrosine to l-dopa in the melanocyte and whether PKC-beta can be described as a rate-limiting enzyme for melanogenesis via its ability to activate tyrosinase. [*ASP* Agouti signaling protein, *6BH₄* (6*R*)-l–erythro-5,6,7,8-tetrahydrobiopterin, *DCT* dopachrome tautomerase, *DHICA* 5,6-dihydroxyindole-2-carboxylic acid, *l-dopa* l-3,4-Dihydroxyphenylalanine, *MC1R* melanocortin 1 receptor, *MSH* melanocyte stimulating hormone, *TRP* tyrosinase-related protein. Adapted from Tobin [71].

tyrosinase-related proteins. Both l-phenylalanine and l-tyrosine can access the melanocyte, the former via the neutral amino acid Na^+/Ca^{2+} ATPase anti-porter system and the latter by facilitated diffusion. l-Phenylalanine is converted to l-tyrosine via phenylalanine dehydroxylase (PAH) activity, and PAH activities have been found to correlate positively with skin phototypes. Melanogenesis regulation also involves hormones, neurotransmitters, cytokines, growth factors, eicosanoids, cyclic nucleotides, nutrients, and the physicochemical milieu [60]. These act sequentially or in parallel, through pathways involving activation of G-protein receptors, receptors coupled to kinase activities or nuclear receptors. The predominant modifier and inhibitor of melanin synthesis in animal (though not in human) hair follicles is agouti protein (ASP) [5]. In mouse the transient synthesis of ASP switches eumelanogenesis to pheomelanogenesis, a change that can be associated with decreased tyrosinase activity [5]. The agouti protein ASP also acts as a direct antagonist to melanocortins and as an inverse agonist at the MC1R [5], being both a qualitative modulator and an inhibitor of melanogenesis. Among the factors modifying ASP action are mahogany (mg) or Attractin (Atrn) (required for ASP action) and mahoganoid (md), also known as Mahogunin (Mgrn1), which prevents hair follicle melanocytes from responding to ASP [21].

Studies have documented that signal transduction pathways involving peptides derived from pro-opiomelanocortin (POMC), SCF/KIT and ET1, ET3/ETA, and ETB play a crucial role in normal follicular melanogenesis [29, 60, 71]. Their pro-pigmentary activity is initiated by the binding of locally produced POMC-derived ACTH, α-MSH, and β-MSH peptides. For example, α-MSH increases the proportion of black to gray hairs when administered intramuscularly in the guinea pig [62]. The cognate receptor of α-MSH is MC1R, an important positive regulator of hair pigmentation [50]. This G-protein-coupled membrane receptor is activated upon binding of POMC-derived ACTH, α-MSH, and β-MSH peptides. The resultant signal transduction cascade activates adenylate cyclase, leading to subsequent cAMP production, which results in increased melanocyte proliferation, melanogenesis, and dendrite formation. However, while injection of α-MSH into human skin increased epidermal melanogenesis, particularly of sun-exposed skin, no effect was seen in hair follicles [38]. This is supported by the failure to detect significant expression of free α-MSH peptide in pigmented human hair bulb melanocytes, in contrast to their epidermal counterparts [33]. Humans with POMC gene mutations may have red-hair phenotype [51].

A POMC/MC1R complementary system, the β-endorphin/µ-opiate receptor system, also participates in the regulation of both human epidermal and follicular melanocyte biology, by inducing changes in dendricity, proliferation, and melanogenesis [32]. The underlying mechanism involved here remains unclear, given that signaling through the µ-opiate receptor results in a downregulation of cAMP [71]. Recently we have also examined the most proximal element of the hypothalamus–pituitary–adrenal axis, i.e., corticotropin-releasing hormone (CRH), in the regulation of melanogenesis. Like POMC, CRH is also produced locally in the human skin [58], and can modify the phenotype of human hair follicle melanocytes in vitro by upregulating cell dendricity and pigmentation levels [34]. The basis for this activity remains to be established, and it could reflect direct (i.e., via CRH receptors) or indirect (i.e., via CRH induction of POMC peptides, e.g., ACTH) effects.

Given the similar biogenic derivation of melanosomes and lysosomes, it is notable that the lack of some lysosomal enzymes can affect the hair follicle pigmentary unit. For example, in the absence of the papain-like lysosomal cysteine protease cathepsin L (CTSL), hair bulb melanocytes can exhibit marked vacuolation during melanosome organellogenesis, suggesting that these organelles may become unstable in the absence of this lysosomal enzyme [82].

4.3.5 Aging of the Follicle Melanocytes and Hair Graying (Canities)

For every decade after 30 years of age the number of pigment-producing melanocytes in exposed/unexposed epidermis decreases by 10%–20% [85], accounting for much of the loss of skin tone with age. Nevertheless, epidermal melanocytes are relatively long-living cells, protected in part from reactive oxygen species (including those generated during melanogenesis) by their high expression of anti-apoptotic cell survival factors, e.g., bcl-2. Hair color shows striking age-related changes, particularly in those of Eurasian origin. During puberty there is often a switch from fair “intermediate” hair to more deeply pigmented, coarser “terminal” hair. Furthermore, hair fiber heterochromia may become more apparent with age, most strikingly for scalp and beard [36]. However, the most dramatic age-related change in hair pigment is the onset of hair graying or canities, which is the gradual age-dependent dilution of hair color to gray or white, also known as senile canities. The increasing longevity of human life inevitably means we will spend an increasing proportion of our lives sporting this sign of lost youth. Canities/graying first appears in our 30s, and so is unlikely to have exerted significant evolutionary selective pressure, occurring as it does after reproductive peak age.

The examination of melanocyte aging has only recently been pursued with any particular vigor. Clinical observation suggests that the follicular- and epidermal-

melanin units have a different "melanogenetic clock." It has been observed that loss of melanocyte replicative potential in vitro is associated not only with increasing age of the donor but also with the melanin content of the cell. This becomes very apparent after long-term continuous exposure to cAMP inducers (e.g., cholera toxin), which induce pigment without directly engaging the MC1R [6]. Similarly, millimolar l-tyrosine (a melanin precursor) abrogates proliferation in cultured "pre-senescent" pigmented melanocytes, with proliferation continuing only in resistant amelanotic cells [6]. On reaching senescence, melanocytes express increased levels of cyclin-dependent kinase (CDK) inhibitors, e.g., p21 and p16, which inhibit cell cycling.

Accumulation of oxidative damage is an important determinant of the rate of cell aging, although it is unclear whether it is the primary cause of aging. It is likely that the antioxidant systems within the hair follicle melanocyte become impaired with age, leading to uncontrolled damage to the melanocyte itself from its own melanogenesis-related oxidative stress. In addition, melanin synthesis, by its very nature, produces mutagenic intermediates. Reactive oxygen species (ROS) can damage DNA (both nuclear and mitochondrial), result in the accumulation of mutations, and can induce both oxidative stress and antioxidant mechanisms. Thus, the induction of replicative senescence in melanogenic hair bulb melanocytes may be an important protective mechanism against cell transformation. The extraordinary melanogenic activity of pigmented bulbar melanocytes (up to 10 years in some scalp hair follicles) is likely to generate large amounts of ROS via the oxidation of tyrosine and dopa to melanin [22]. If not adequately removed, an accumulation of these ROS may generate significant oxidative stress in both the melanocyte itself and in the highly proliferative anagen hair bulb epithelium. Thus, in these circumstances, melanogenic bulbar melanocytes are perhaps best suited to assume a post-mitotic, terminally differentiated "(pre)senescence" status to prevent cell transformation. Recent work suggests that the follicular–melanin unit of graying hair is associated with increased melanocyte apoptosis and oxidative stress [4]. Moreover, this study also reported that the "common" deletion in mitochondrial DNA (associated with oxidative stress) occurred more prominently in graying compared to normally pigmented hair follicles. Graying hair follicles were also less well equipped to handle an exogenous oxidative stress, which is likely to be the result of impaired antioxidant mechanisms.

A characteristic feature of bulbar melanocytes is their extremely high melanin load and phenomenal synthetic capacity for melanin production (Fig. 4.2). A relatively small number of melanocytes (<100 cells per scalp anagen hair follicle) can, in a single hair growth cycle, produce sufficient melanin to intensely pigment up to 1.5 m of hair shaft. Moreover, they do this within the context of a melanin-laden cell cytoplasm. In this way, hair bulb melanocytes are very different from melanogenically active epidermal melanocytes, which retain few fully mature melanosomes in their cytoplasm at any one time. This intrinsic ability of bulbar melanocytes to "pool" melanin internally may make them more vulnerable than epidermal melanocytes to the toxic elements of melanogenesis.

The synthetic capacity of bulbar melanocytes is greatest during youth when the scalp follicular melanin unit is only a few cycles old and is able to make use of the full post-puberty hormonal stimulus. On average, an individual scalp hair follicle will experience fewer than 15 melanocyte seedings from the presumptive reservoir in the outer root sheath to the hair bulb in the average fully "gray-free" life span of 35 years for Caucasians [35]. Interestingly, repeated plucking of hair from vibrissae follicles leads to the eventual re-growth of gray hair [27], again suggesting limited capacity of the pigmentary reservoir. However, the associated tissue injury during plucking complicates the interpretation of this finding. In any event, the onset and progression of hair graying correlates closely with chronological aging and occurs to varying degrees in all individuals, regardless of gender or race. Age of onset also appears to be genetically controlled and inheritable. Thus, the average age for Caucasians is mid-30s; for Asians, late-30s; and for Africans, mid-40s. Similarly, hair is said to gray *prematurely* if it occurs before the age of 20 in whites, before 25 in Asians, and before 30 in Africans. A good rule of thumb is that by 50 years of age, 50% of people have 50% gray hair. Clearly, the darker the hair, the more noticeable early graying will be. However, graying can be more extensive in dark hair before total whitening is apparent; the reverse is true for blond hair. Graying first appears usually at the temples, and spreads to the vertex and then the remainder of the scalp, affecting the occiput last. Beard and body hair is usually affected later. Graying often follows a wave that spreads slowly from the crown to the occiput.

4.3.5.1 Histopathology of Canities

"Gray" hair may in most cases be illusory – an impression of gray provided by the admixture of fully white and fully pigmented hair. Here unpigmented hair grows in as a white hair fiber. However, canities can also affect individual hair follicles (Fig. 4.6) part way through anagen VI. This hair-follicle-specific change may result in either a gradual loss of pigment over time and over several cycles or a gradual loss of pigment along the same hair shaft (i.e., within the anagen phase of a *single* hair cycle). While few pigment granules are present in truly

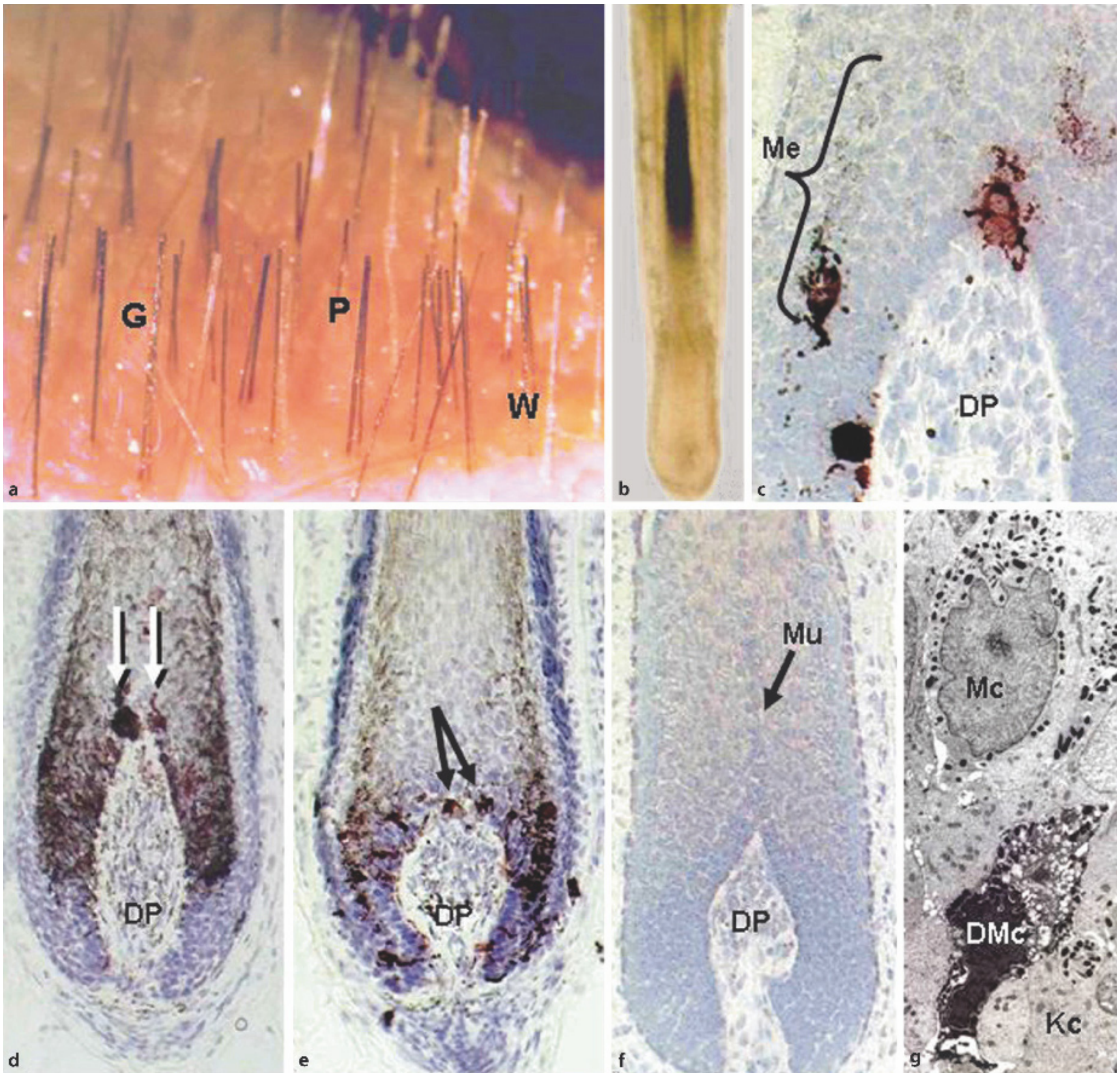


Fig. 4.6a–g Histopathology and ultrastructure of canities in human scalp hair follicles. **a** Macroscopic view of graying scalp showing admixture of white (*W*), gray (*G*), and pigmented (*P*) hairs. **b** Intact gray/white hair follicles isolated from human scalp specimen. **c** Immunohistochemistry of graying human scalp hair bulb showing gp100-positive melanocytes. These melanocytes are hypertrophic with blunted dendrites. Note presence of melanin granules (*Me*) transferred to precortical keratinocytes (*curly braces*). (*DP* follicular dermal papilla.) **d–f** Progression of melanocyte loss (*left* to *right*) from three adjacent anagen hair follicles in human scalp. Note pigment dilution is greatest in central regions of the hair shaft, reflecting an apparent heightened sensitivity of melanocytes in this region. (*Mu* Medulla.) **g** Transmission electron micrograph of a section of anagen hair bulb during progression of canities. Note presence of degenerative (*DMc*) and adjacent normal appearing (*Mc*) melanocytes. (*Kc* Keratinocyte.)

white hair shafts, melanin granules can be readily detected within the precortex of gray hair follicles.

Pigment loss in graying hair follicles is due to a marked reduction in melanogenically active melanocytes in the hair bulb of gray anagen hair follicles. A true gray hair bulb shows a much reduced, yet detectable, dopa reaction (tyrosinase activity), while white hair bulbs are broadly negative. However, there also appears to be a specific defect of melanosome transfer in graying hair follicles, as keratinocytes may fail

to contain any melanin granules despite being close to melanocytes with a moderate number of melanosomes (Tobin unpublished observations). Further evidence of a defective melanocyte–keratinocyte interaction is suggested by the presence of melanin debris in the graying hair bulb (Fig. 4.6) and surrounding dermis. Moreover, residual hair bulb melanocytes in canities-affected hair follicles are often hypertrophic (Fig. 4.6c), although this may reflect a reduction in dendricity rather than an overall increase in cell volume. Moreover, melanosomes are often packaged within autophagolysosomes suggesting that these melanosomes are defective, perhaps even leaking reactive melanin metabolites. Autophagolysosomal degradation of melanosomes is usually followed by death of the melanocyte itself [53]. The involvement of ROS in the histopathology of canities is supported by the observation that melanocytes in graying and white hair bulbs may be vacuolated, a common cellular response to increased oxidative stress. Degenerative change in canities-affected hair bulbs (Fig. 4.6c–g) can resemble apoptosis and is reminiscent of melanocyte degeneration in alopecia areata where pigmented hair follicles are preferentially targeted by an aberrant immune response (Fig. 4.7b).

Loss of melanocytes can apparently occur very rapidly from canities-affected hair bulbs, as suggested by melanin located in the follicular papilla and/or connective tissue sheath of hair follicles that lack any morphologic evidence of melanogenesis or melanocytes in their hair bulb. This presence of pigment debris in gray/white hair follicles would appear to indicate a recent loss of previously melanogenic melanocytes. The removal of melanogenic melanocytes from the hair bulb of graying and white hair follicles may also be associated with a parallel increase there of dendritic cells including Langerhans cells. Re-location of these antigen-presenting phagocytic cells from the upper hair follicle may be in response to antigens released from, or expressed on, degenerating canities-affected melanocytes.

4.3.5.2 Impact of Melanocyte Loss on the Hair Follicle

Given their close physical interaction, it is likely that bulbar melanocytes influence precortical keratinocyte behavior in several ways. Melanin transfer to keratinocytes appears to reduce their proliferative potential and increase their terminal differentiation. Indeed, white beard hair has been shown to grow faster than adjacent pigmented hair, and unpigmented hair follicles exhibit a higher rate of hair fiber elongation than matched pigmented hair follicles in vitro [4, 41]. In this way melanosomes may act as "regulatory packages" [56], e.g., providing a buffer for calcium with resultant implications for second messenger/cell signaling in melanogenesis, melanosome transfer, and keratinocyte differentiation. Furthermore, the saturation binding of transition metals (e.g., iron, copper) to melanin provides effective antioxidant defense for the melanosome-receiving keratinocyte. Melanocytes may also influence neighboring keratinocytes via the production of various cytokines, growth factors, eicosanoids, adhesion molecules, and extracellular matrix [67]. Further clinical evidence of melanocyte–keratinocyte interactivity may be the basis of the coarser, wirier, and more unmanageable nature of gray/white hair compared to pigmented hair, reflecting their different chemical and physical properties [83]. Indeed, gray hair is often unable to hold a set and is more resistant to incorporating artificial color. Moreover, it appears that the aging hair follicles can reprogram their matrix keratinocytes to increase the production of medullary, rather than cortical, keratinocytes.

4.3.5.3 Spontaneous Re-Pigmentation of Hair in Canities

Spontaneous scalp hair re-pigmentation has been reported after radiation therapy for cancer or after inflammatory events, e.g., erythrodermic eczema, and erosive candidiasis of the scalp (c.f. [82]). Reversal of canities here is likely to result from radiation/cytokine-induced activation of melanoblasts residing in the outer root sheath melanocyte reservoir, and so raises the attractive possibility that these melanocytes may be targeted to naturally re-pigment graying hair follicles. Another clinical scenario that provides an insight into both the pathomechanism of canities and possibilities for pigment recovery is the not too uncommon partial spontaneous reversal of canities that occurs during its early stages. Here, melanogenesis in de-activated bulbar melanocytes may re-start during anagen VI of the same hair growth cycle (c.f. [82]).

4.4 Clinical Relevance of Hair Pigmentation

Recent reports linking, albeit not causally, cigarette smoking with premature gray [14] have raised the specter of canities as a marker for general health status. A possible explanation of the above phenomenon may be that smoking-related diseases increase aging of many body systems including pigmentation. However, more

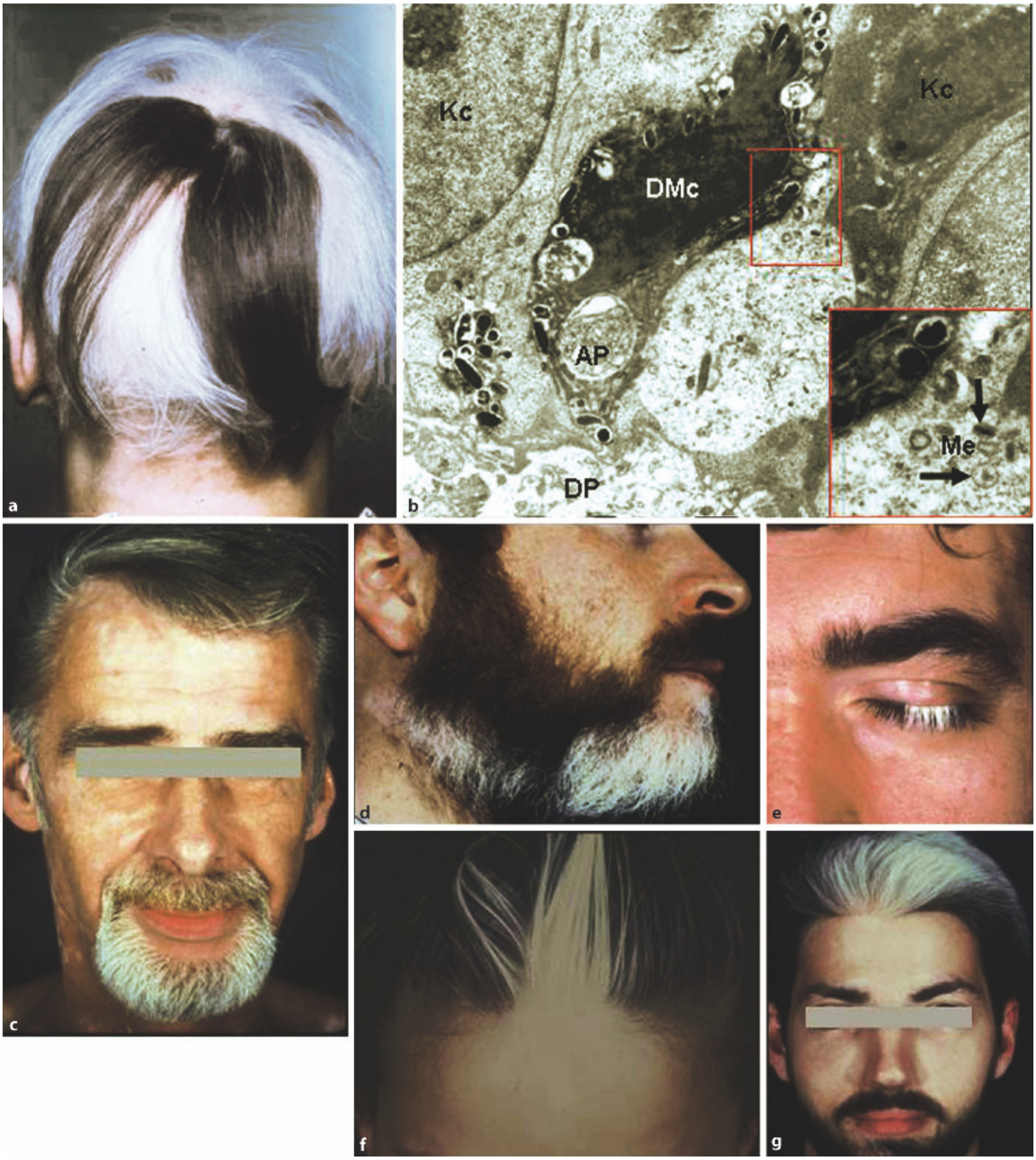


Fig. 4.7a–g Examples of common pigmentation disorders of the hair follicle. **a** White hair regrowth in alopecia areata-affected woman (image courtesy of Dr David Fenton). **b** Degenerating melanocyte (*DMc*) in the anagen hair bulb of a patient with acute alopecia areata. (*AP* autophagolysosome, *DP* follicular dermal papilla, *Kc* keratinocyte, Me (pre)melanosomes) **c** Co-expression of canities and vitiligo (e.g., neck region) in a middle-aged man. **d** Circumscribed poliosis due to vitiligo affecting both epidermal and follicular pigmentation in a young man. **e** Leukotrichia due to vitiligo limited to the eyelashes in a young man. **f** White forelock characteristic of piebaldism in a young women. **g** White forelock in a young man with Waardenburg syndrome. Reproduced with permission from Tobin et al. [77]

direct effects, e.g., via smoke genotoxin-induced apoptosis, may also be involved. Whether canities, premature or otherwise, is a predictor/risk marker for disease remains controversial, largely due to poor study design. If it exists at all it is more likely to reflect associated genetic effects rather than direct linkage. It has been reported that individuals with premature canities (with no other identifiable risk factor) were more likely to develop osteopenia than individuals without canities [52]. A subsequent study found that people who grayed before their 20s has lower bone mineral density compared to those who grayed later. Some have concluded that premature graying could account for a small fraction of the variance in bone mineral density within the population [46]. Even less clear are the purported associations between early onset of gray hair and cardio disease or studies showing graying of hair as additional risk factors for myocardial infarction.

4.4.1 Disorders Affecting the Hair Follicle Pigmentary Unit

Pigmentation disorders of the hair follicle include: acquired, endogenously induced hypomelanoses including acquired poliosis (e.g., alopecia areata and vitiligo), genetic hypomelanoses (e.g., albinism) and circumscribed poliosis (e.g., piebaldism, Waardenburg syndrome), and endocrine-associated hair color dilution (e.g., homocystinuria, and sometimes in phenylketonuria). Although a detailed treatment of the many disorders with hair color defects is beyond the scope of this chapter [72], it is nonetheless useful to consider the involvement of the follicular melanin unit in the pathogenesis of a few common dermatoses.

4.4.1.1 Alopecia Areata

The literature contains many references to historic characters afflicted by sudden loss of hair color (e.g., Shah Jahan, Marie Antoinette, Thomas Moore, etc.), especially during dramatic periods in their lives. Anxiety of a more chronic type has been used to explain early graying, and "turning white over night" (*canities subita*) is anecdotally associated with episodes of acute fear or grief. Acute alopecia areata is now considered to be the most likely explanation of this sudden whitening, as here pigmented hair is often preferentially targeted while white hair is relatively spared [70, 73] (alopecia areata, see Chap. 15). Pigmented bulbar melanocytes undergo frank degenerative change in acute alopecia areata (Figs. 4.7b) [73]. Immunologically, patients with acute disease may produce antibodies to cytoplasmic antigens expressed in cultured hair follicle melanocytes [74], and T cells from the scalp of alopecia areata patients are induced to proliferate in response to pigment cell antigen [19]. It has been suggested that the anagen hair bulb in alopecia areata loses its usual "immune privilege," becoming positive for major histocompatibility complex (MHC) class I antigens [10, 30, 87]. Thus, some melanogenesis-associated proteins may trigger an anti-pigmented hair follicle immune response during anagen III/IV due to antigen leakage [47]. Another alopecia-areata-associated pigmentary anomaly is the re-growth of white hair (Fig. 4.7a), which usually recovers its original color in time. This delay in re-pigmentation may reflect a slow recovery from severe damage in the hair pigmentary unit that may have reduced the total number of available melanocytes in the hair follicle, including in the presumptive outer root sheath precursor pool. Alternately, a permissive environment for melanogenesis, involving for example integrins, may not return immediately until full recovery of the keratinocyte population.

4.4.1.2 Vitiligo

This de-pigmenting disorder is usually focused on the epidermis but can also occasionally lead to leukotrichia in the depigmented skin (leukoderma) (Fig. 4.7c–e). It may result from severe oxidative stress in skin. While the status of hair bulb melanocytes in vitiligo-associated human leukotrichia has not been formally investigated, hair bulb melanocyte necrosis occurs in a vitiligo mouse model, the C57BL/6Jler-vit/vit mouse [8]. Spontaneous (or induced) re-pigmentation of the epidermis is rare in vitiligo; when it happens, the consensus is that outer root sheath melanocytes proliferate and then enter the epidermis [13]. However, re-pigmentation may also occur via the epidermis itself. Despite current dogma, a small number of poorly differentiated melanocytes are retained in lesional epidermis, even after vitiligo of long duration [81]. Leukotrichia and canities can co-exist in aging individuals (Fig. 4.7c).

4.4.1.3 Circumscribed Poliosis

Poliosis is the general term to describe an inherited or acquired loss of pigment from a group of closely positioned hair follicles resulting in a patch of white/hypopigmented hair. It can be seen in vitiligo, piebaldism, Waardenburg, Vogt–Koyanagi–Harada, Griscelli and Apert syndrome. Piebaldism, an autosomal dominant genetic disorder, is characterized by a white forelock associated with diamond-shaped depigmentation on the forehead and is associated with impaired melanocyte maturation/migration in affected hair bulbs (reviewed in [63]) (Fig. 4.7f). Focal mutations or deletions in the

KIT gene (encoding SCF receptor) have been identified. Molecular studies of Waardenburg type I syndrome also reveal mutations/deletions in KIT, whereas the *MITF* (microphthalmia transcription factor) gene is deleted in Waardenburg type II syndrome [63]. Reduced eumelanogenesis and melanocyte loss is observed in Prader-Willi and Angelman syndromes where pink-eyed dilution gene deletions occur. Waardenburg syndrome type I–III can present with sensorineural deafness, partial or total heterochromia irides, dystopia canthorum, and eyebrow hyperplasia with synophrys, and piebaldism (Fig. 4.7g) in addition to premature graying.

4.4.1.4 Genetic Poliosis

Albinism consists of a group of autosomal recessive diseases that exhibit the congenital reduction or absence of melanin in skin, hair, and eyes (reviewed in [45]). The hair and skin color can be affected to various degrees, ranging from complete white hair to red, brown, and dark hair. The rare Chediak-Higashi syndrome is additionally characterized by the production of silver gray/light blond hair on the scalp.

4.5 Experimental Techniques

Melanocytes have proven to be fastidious in their culture requirements. Thus, most of the pre 1980s pigment cell literature is limited to melanoma studies, with speculative extrapolations of normal pigment cells. However, a breakthrough came when Eisinger and Marko observed that melanocytes have a fundamental double mitogen requirement in order to proliferate in vitro and identified two artificial mitogens, phorbol ester and cholera toxin [16]. Subsequently, natural melanocyte mitogens were discovered in bovine brain extracts [86] and now basic fibroblast growth factor and endothelin-1 can be used to replace artificial mitogens [20, 89]. Most published studies still report the continued use of artificial mitogens in melanocyte culture.

4.5.1 Hair Follicle Melanocyte Culture

The study of in vitro hair pigmentation has, however, languished behind that of epidermal pigmentation. Initial studies of hair follicle melanocytes in vitro were restricted to incubations of isolated hair follicles with different reagents to assess effects on total melanin production within the hair bulb [40]. About a decade ago we successfully isolated and cultivated human scalp hair follicle melanocytes for growth in long-term culture in the presence of a phorbol ester and cholera toxin in addition to bovine pituitary extract [74]. Using this methodology, we identified follicular melanocytes of several different types, some of which differed significantly from cultured epidermal melanocytes isolated from the same scalp specimens [69]. Hair follicle melanocytes can now be routinely (relatively) isolated from fresh normal haired skin and grown in medium containing natural mitogens [31], though it is important to avoid contamination from epidermal or infundibular melanocytes. Single cell suspensions of total hair follicle cells are obtained by treating isolated hair follicles with trypsin/ethylenediamine tetraacetic acid (EDTA). The follicular cells can be plated onto small plastic tissue culture dishes with Eagle's MEM supplemented with 5% fetal bovine serum, 5 ng/ml endothelin-1, 5 ng/ml basic fibroblast growth factor and keratinocyte serum-free medium containing 25 µg/ml bovine pituitary extract and 0.2 ng/ml recombinant epidermal growth factor (rEGF). When present, contaminating fibroblasts can be removed with short-term Geneticin treatment (c.f. [31]) and keratinocytes can easily be removed by differential trypsinization.

Many hair follicle melanocytes appear amelanotic and fibroblastic in early cultures and may stain negative for melanocyte-specific markers (Fig. 4.8a) [69]. Melanogenically active melanocytes from the anagen hair bulb make up only a very small proportion of cells in the suspension and are easily recognized by the intensely pigmented and variably dendritic phenotype. Proliferation is only usually seen in the weakly differentiated or undifferentiated follicular melanocytes after the first 7–10 days in primary culture (Fig. 4.8b). Amelanotic follicular melanocytes can be induced to pigment with addition of cAMP inducers, e.g., the phosphodiesterase inhibitor 3-isobutyl-1-methylxanthine.

4.5.2 Whole-Organ Hair follicle Ex Vivo Culture

Intact anagen VI hair follicles (Fig. 4.8b) can now be maintained with elongating hair fibers in ex vivo culture for periods up to 10 days [49], and so provide much opportunity to examine different subpopulations of follicular melanocytes in their normal three-dimensional environment. Indeed, results to date indicate that melanocytes of the follicular melanin unit appear to be more sensitive than surrounding proliferating matrix keratinocytes in this system (Tobin, unpublished data). Different test agents may be applied to the medium to stabilize this population. Melanocyte movement/migration can also be assessed using these cultures (Fig. 4.8c–e), and is likely to provide a wealth of highly relevant data over the coming years.

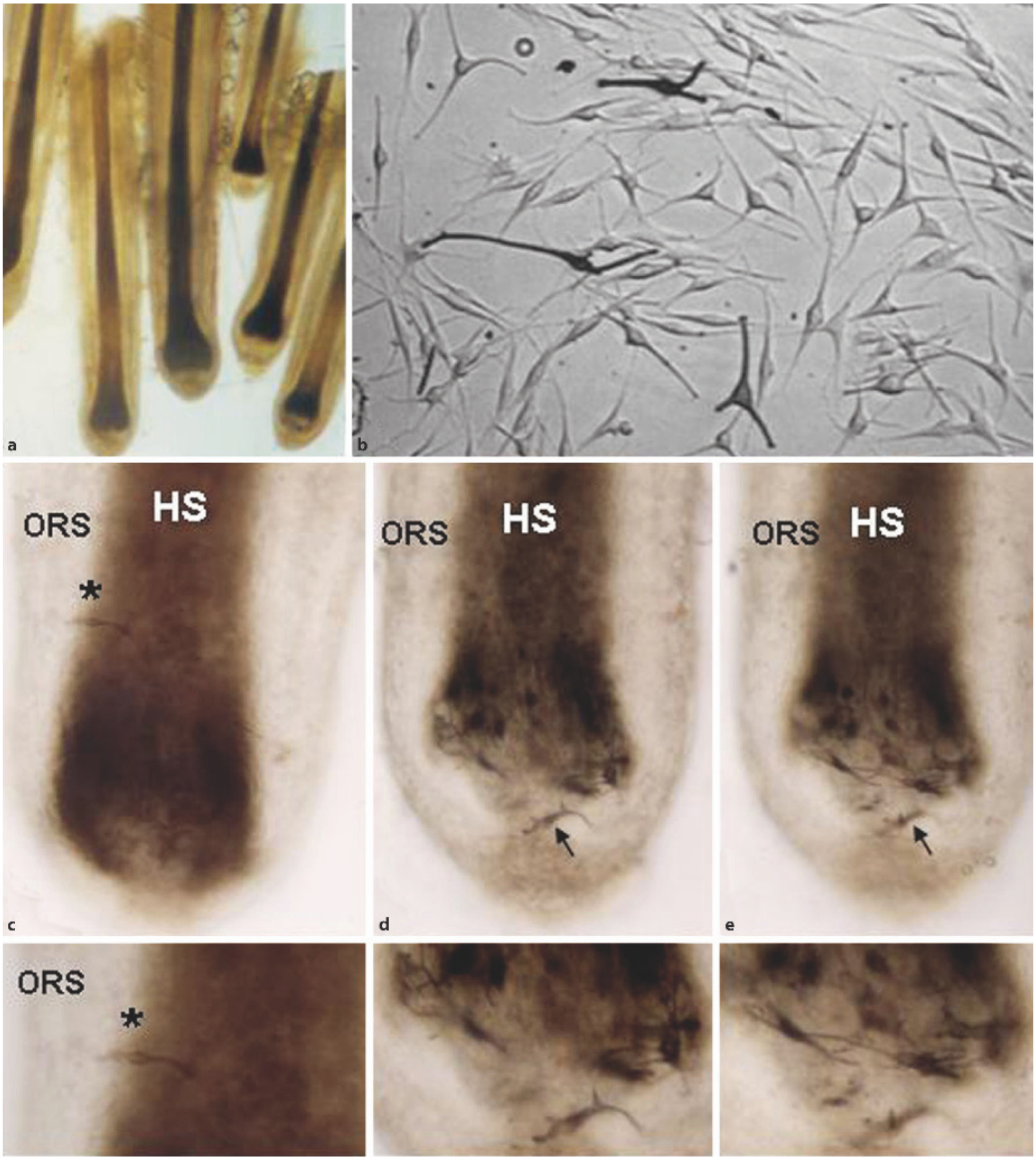


Fig. 4.8a–e Study of hair follicle pigmentation using in vitro assays. **a** Intact anagen VI hair follicles isolated from human scalp tissue. **b** Primary culture of hair follicle melanocytes. Note pigmented bulbar melanocytes and amelanotic outer root sheath melanocytes. **c–e** Assessment of hair bulb melanocytes during ex vivo hair follicle cultures. Note migration of melanocytes from the melanogenic zone (*arrows*) after 3 days in culture, some towards the outer root sheath (*)

4.5.3 Delivery of Agents to the Hair Follicle

A significant operational issue to be addressed in hair follicle pigmentation studies will be the optimal delivery of relevant reagents (e.g., protein or genes) to the hair follicle and particularly to appropriate regions of the hair follicle. The last 10 years has seen significant advances in the selective delivery of peptides and genes into the skin [2] and pilosebaceous units [1, 23, 84]. These have indicated that the hair follicle offers a particularly safe and noninvasive route for gene delivery, including for pigmentation research [3, 23, 89]. To date it has been reported that the albino point mutation in the tyrosinase gene has been "corrected" in a small number of murine follicles using an RNA-DNA chimeric oligonucleotide [3]. In these experiments, liposomes were more specific than injection in their delivery of the oligonucleotides to the hair follicle, although liposomes showed lower efficiency. Using a somewhat different approach, Hoffman's laboratory induced melanin production in albino mouse skin histoculture using a recombinant retrovirus containing the mel locus of *Streptomyces antibioticus* (pLmelSN retrovirus). Melanin was observed in approximately 60% of albino-mouse hair follicles after 1 week in histoculture, indicating that the *S. antibioticus mel* operon expresses an active tyrosinase [90].

While these studies are exciting and lay an excellent foundation for further studies, there is a fundamental difference between albino melanocytes and canities-affected melanocytes: the former may contain all melanogenesis-related machinery with the sole exception of active tyrosinase. Therefore, it is likely that several sites in the melanogenesis-permissive microenvironment will need to be targeted in canities. Nonetheless, the adaptation of the above technology to canities could theoretically be applied. We need to approach this cautiously however, as alteration of melanocyte activity in human skin may affect not only follicular melanocytes but also those in the epidermis and sebaceous glands. Application to human canities will also require very high efficiencies involving high numbers of hair follicles to be of any cosmetic value.

4.6 Outlook – Future Developments

4.6.1 Is Canities Reversible?

The function of amelanotic melanocytes distributed in the outer root sheath of human scalp hair follicles (including those of the so-called stem cell compartment) is in great need of investigation. These cells are clearly available for re-pigmentation/repopulation of the epidermis if necessary (e.g., after wounding) [64]. Their lack of direct contribution to hair pigmentation may indicate that their status in the senile white hair follicle is no longer permissive for migration to the melanogenic zone during early anagen, as apparently occurs in pigment-producing hair follicles. Some insights into possible roles for outer root sheath amelanotic melanocytes have been garnered from increasingly convincing anecdotal reports of induced scalp hair re-pigmentation after radiation therapy for cancer (c.f. [68]) or after inflammatory events, e.g. erythrodermic eczema and erosive candidiasis of the scalp (c.f. [68]). Here, reversal of canities is likely to result from radiation/cytokine-induced activation of outer root sheath melanocytes. This raises the attractive possibility that these melanocytes may be induced to migrate and differentiate to naturally re-pigment graying hair follicles. This finding also suggests that the cytokine milieu may be alterable to provide for a permissive microenvironment for melanocyte migration and activation. Temporary hair darkening has been reported after large doses of para-aminobenzoic acid, though it is not clear whether the increased pigmentation was directly related to enhanced hair bulb melanocyte activity. By contrast, study of hair follicles during spontaneous re-pigmentation seen at the early stages of canities may provide several clues to help us identify the subtle changes in the hair follicle's repository of melanoblasts and pigment-producing melanocytes of the melanogenic zone in the hair bulb.

The deficit in canities-affected hair follicles is likely to be multi-factorial, including the loss of migratory stimuli, particularly during the critical stages of the hair cycle when cell–cell and cell–matrix interactions are highly active. Several factors could theoretically be administered to canities-affected scalp. Basic fibroblast growth factor, leukotriene C4 and endothelin-1 are potent chemotactic (i.e., directional in concentration gradient) factors at least in Boyden chamber-type in vitro studies [25]. Along with another potent melanocyte migration factor, stem cell factor, these molecules regulate the expression of integrins on the surface of several cell types including melanocytes themselves. Clearly, the sequential regulation of integrin expression will be critical for melanocyte migration in the hair follicle. These growth factors are produced in the skin by keratinocytes (basic fibroblast growth factor, endothelin-1) and by fibroblasts, including the optimally located dermal papilla fibroblasts (SCF, leukotriene-4) [20, 28]. Indeed, SCF and its receptor KIT have been directly implicated not only in the migration (via chemokinesis rather than chemotaxis) of melanoblasts into the hair follicle but also their survival and proliferation. The POMC family of peptides (α-MSH, ACTH, β-endorphin, etc.) is another group of agents that stimulate hair pigmentation via both autocrine and paracrine routes. Thus, it is unlikely that any single factor will ensure directional

Table 4.1 Keywords and explanations

Dopa-negative melanocytes	Melanocytes in which the tyrosinase protein lacks enzyme activity to oxidize 3,4-dihydroxyphenylalinine (dopa) to dopaquinone
Dopa-positive melanocytes	Melanocytes in which the tyrosinase protein has enzyme activity to oxidize 3,4-dihydroxyphenylalinine (dopa) to dopaquinone
Epidermal-melanin unit	A unit of one melanocyte and approximately 36 viable keratinocytes originally proposed by Fitzpatrick and Breathnach [17] that accepts, transports, metabolizes, and degrades melanin granules obtained from this melanocyte. A correlate in the hair follicle has been termed *follicular-melanin unit* [79] consisting of one melanocyte to approximately five keratinocytes at the basal lamina separating the follicular papilla and epithelial matrix in the anagen hair bulb. Follicular melanin units may overlap
Eumelanosomes	Ellipsoidal melanosomes producing predominantly brown/black melanins
Melanin	A high-molecular-weight biological pigment found in skin, hair, feathers, scales, eyes, and some internal membranes formed as an end-product during metabolism of the amino acid tyrosine. Operationally grouped as *eumelanin* (dark brown-black insoluble nitrogenous pigment derived from oxidative polymerization of 5,6-dihydroxyindoles derived from tyrosine) and *pheomelanin* (yellow-red alkali-soluble sulfurous pigment derived from oxidative polymerization of cysteinyldopas)
Melanoblast	Precursor melanocyte
Melanocyte	Mature pigment-forming cells in mammals
Melanogenesis	The melanin biosynthetic pathway in living cells characterized by a complex multi-step process involving multiple substrates, enzymes, and cofactors that commence with phenylalanine/ tyrosine and end with complex polymeric melanins deposited on a protein matrix within the melanosome. The rate-limiting enzyme in melanogenesis is tyrosinase. Full consensus is still lacking with regard to some elements of this biochemical pathway
Melanophage	Dermal macrophage with internalized melanin. Note: fibroblasts of the follicular papilla and dermal connective tissue sheath can take up melanin, especially during catagen
Melanosome	Membrane-bounded cytoplasmic organelle (related to lysosomes) unique to melanocytes (and melanophores in non-mammals) that when mature (i.e., enzymatically active, stage IV) can synthesize melanins
Pheomelanosomes	Spherical melanosomes producing predominantly yellow/red melanins
Pre-melanosomes	Immature variant of the melanosome (i.e., stage 0–III) characterized by lack of/or partial production of melanin
Stem pigment cell	Committed melanocyte lineage cell with unlimited self-renewal properties

movement within the complex microenvironments of the cycling adult hair follicle.

Summary for the Clinician

Despite the massive contribution to pigmentation sciences made by the study of the murine follicular–melanin unit, the field of hair follicle pigmentation has lagged significantly behind that of the epidermis. Now that we have overcome some of the more significant technical hurdles we should now be able to make rapid progress toward elucidating the regulatory mechanisms controlling hair pigmentation in the human hair follicle. Prominent amongst these will be a focus toward the aging hair follicle and a full exploration of the maximal potentiality of hair follicle melanocyte populations. Correcting genetic pigmentation disorders may also be feasible via more efficient delivery of appropriate genes to melanocytes stem cells. Our developmental biology colleagues will also generate relevant new data as they continue to exploit the unique accessibility provided by the hair follicle to answer general developmental biology questions. The future looks bright for hair pigmentation sciences.

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Chapter 5

Hair Follicle Vascularization and Innervation

5

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Synonyms
nerves, blood vessels, vasculature, endothelial cells

Key Features

- Advances in immunohistochemical techniques and the development of antibodies specific for nerves, neuropeptides, lymphatics and endothelial cells have given investigators the opportunity to visualize all cutaneous nerves endothelial and endothelial-derived cells.
- The use of confocal laser scanning microscopy offers additional sensitivity and the ability to view cutaneous structures in three dimensions.
- The development of mouse mutants with functional deletions or overexpression of genes coding for neurotrophins, neuropeptides, their receptors, or endothelial cell proteins provides the tools for elucidating the significance of piloneural, piloendothelial or neuroendothelial interactions.
- Neural/endothelial/pilar interactions can now be examined with many different types of techniques.

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5.1 Introduction

The role of the follicular vasculature in hair diseases has been queried for decades and still many patients, particularly those with androgenetic alopecia, question whether their follicles are getting enough blood/nutrients [9]. More recently, the role in hair disease [9, 19, 21,22] of the peripheral nervous system and associated neuropeptides such as substance P (SP), calcitonin gene related peptide (CGRP), vasoactive intestinal peptide, neuropeptide Y and others has been examined. The expression of neuropeptides and neuropeptide receptors by nerves as well as immune cells provides a communication between the peripheral nervous system, the central nervous system and the skin immune system;

a communication that can be altered in the diseased state. Adding to this complexity is the recent appreciation of lymphatic endothelial cells surrounding the human hair follicle. In this chapter, the innervation and vasculature of the human hair follicle will be reviewed.

5.2 History

Montagna and Ellis [22] described the vascularity and innervation of the hair follicle in an excellent article published in 1957. They described hair follicles as being surrounded by a dense and continuous plexus of capillaries with different patterning in active versus quiescent follicles. In 1952, Gomori [13], using primarily the azo-dye technique for alkaline phosphatase, detailed the vasculature of the hair follicle. The lower third of the anagen follicle has been described as being enveloped in a rich vascular network composed of parallel vessels connected by cross shunts. From the area just above the bulb to the level of the sebaceous gland, most of the cross shunts drop out and the follicle is surrounded by parallel longitudinal vessels. At the level of the sebaceous glands the vessels have been described as forming a network around the glands and then terminating in a loose network at the surface of the skin. Vellus follicles were described as being surrounded by a very simple capillary system whereas resting follicles are surrounded by a palisade of capillaries connected by short, transverse vessels [30].

These observations have been confirmed with the use of modern technology using immunohistochemical techniques and confocal microscopy. An image of the vasculature of the lower region of an anagen hair follicle obtained using immunohistochemical techniques and laser scanning confocal microscopy is presented in Fig. 5.1. The intricate rich vascular supply of the lower third of a human anagen hair follicle is presented, demonstrating the features that Montagna and Ellis [22], and Gomori [13] initially described.

Montagna and Ellis [22], as well as Schmit and Winkelmann [36] ascertained the follicle's innervation using a cholinesterase technique and silver and methylene blue stains. Like the vasculature, the nerve supply to hair follicles was found to vary with the size of th

e follicle. In general, myelinated nerves from the deep dermis form the perifollicular plexus of nerves with some of the fibers running parallel to the follicle, and others forming a net around the follicle. At the bulge region of large follicles and at the level of the bulb of small and vellus follicles, nerve fibers were described as forming a stockade-like structure encircling the follicle. The end organs of the perifollicular longitudinal nerves were described as being composed of swollen axons and nonmyelinated Schwann sheaths.

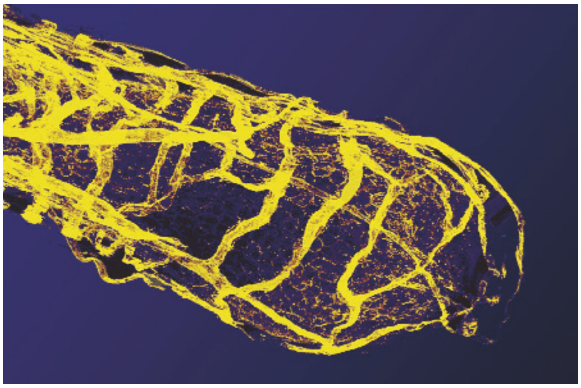


Fig. 5.1 Vascular network encasing the hair bulb of the anagen human scalp hair follicle. Blood vessels of this 200-µm-thick section were stained with the plant lectin, *Ulex europeaous*, conjugated to fluorescein. Image was captured using laser scanning confocal microscopy (100 × magnification)

It has been demonstrated that innervation changes during the hair cycle in mice, with circular nerves increasing in number during the early stages of anagen. Similar changes remain to be demonstrated in the human hair cycle [6]. Much of this earlier work on hair follicle innervation has been corroborated recently in studies utilizing newly developed antibodies, immunohistochemical techniques, and confocal microscopy. The use of these techniques has allowed investigators to simultaneously visualize the innervation and the vasculature of the follicle. The ability to label a third marker has also permitted immunohistochemical analysis of other proteins such as the neuropeptides SP or CGRP and to visualize their association with nerves or vessels in three dimensions in normal or diseased skin.

Using these techniques, a picture of the innervation and vasculature of a human scalp anagen hair follicle is presented in Fig. 5.2. The close association and complexity of the hair follicle's innervation and vasculature are demonstrated. It is interesting to also note that there is minimal co-localization of perifollicular nerves and blood vessels and each appears to have an independent perifollicular organizational structure.

5.3 Structure and Function/ Pathophysiology/Developments

The skin is one of the most densely innervated mammalian organs, permitting it to serve multiple functions

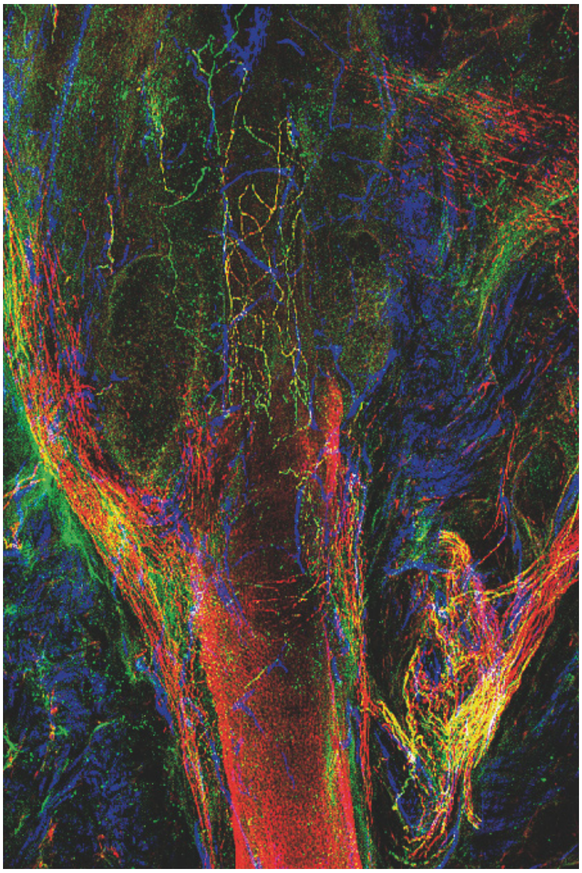


Fig. 5.2 Confocal image projection of the nerves, neuropeptide (calcitonin gene related peptide or *CGRP*), and vessels of the bulge/stem cell region of a human anagen scalp hair follicle. A 4-mm punch biopsy specimen was acquired from a 44-year-old Caucasian male, and then fixed and vertically sectioned into 200-µm-thick sections. The sample was multi-stained to visualize the nerves (PGP9.5, *red*), sensory neuropeptide (CGRP, *green*) and vasculature (*Ulex-europeaous* FITC, *blue*). The inner longitudinal array of perifollicular nerves, the outer circular and vertical nerves as well as innervation of the arrector pili muscle are demonstrated. The image was constructed from 100 optical sections acquired at 1.0-µm intervals, projected in register (100× magnification)

[14, 27]. For example, cutaneous blood vessels as well as other skin appendages are simultaneously innervated by sympathetic, sensory, and parasympathetic axons. The major function of somatic cutaneous axons is sensation, with each type of sensory receptor transducing specific forms of energy into action potentials notifying the brain/central nervous system about environmental agents.

Sensory axon fibers are morphologically classified as either myelinated (A-fibers) or unmyelinated (C-fibers). A-delta fibers are an intermediate, thinly myelinated class. Epidermal nerves are generally categorized as either peptidergic or nonpeptidergic, with the neuropeptide CGRP believed to be universally present in peptidergic nerves along with other neuropeptides. In the spinal dorsal horn, CGRP-positive cutaneous sensory neurons have been described as projecting to adjacent but distinct superficial laminae, indicating that the central nervous system has the capability of identifying when the epidermis has been stimulated and to what depth [23].

Efferent innervation of the skin is usually mediated by the contents of vesicles that distend the thin intracutaneous axons thereby influencing adjacent cells. There are also other effectors, including monoamines, purines, amino acids, nitric oxide, various peptides, SP, CGRP, neurokinin A, vasoactive intestinal peptide, neuropeptide Y, histamine, calretinin, serotonin, and somatostatin [8].

Classical physiology and neuroanatomy continue to define cutaneous nerve fibers as either afferent in terms of autonomic function, or efferent in terms of sensitivity as described previously. However, the subsequent discovery of neuropeptides within the peripheral nervous system prompted a change in the concept of brain–skin communication. One such neuropeptide, SP, influences the function of immune cells such as CD4+ and CD8+ lymphocytes, macrophages, and mast cells [27].

5.3.1 Substance P

Substance P is best known for its role in pain transmission but it also has several other functions, some of which may be involved in hair diseases. Substance P can induce mast cell degranulation as well as the expression of endothelial-leukocyte adhesion molecule-1 on adjacent venular endothelial cells. Substance P enhances DNA synthesis by human peripheral blood lymphocytes and can stimulate mononuclear and polymorphonuclear leukocyte chemotaxis. The effect of SP has been examined on the back skin of telogen mice by investigating whether this neuropeptide can induce hair growth. Capsaicin was injected intradermally or slow release formulations of SP were implanted subcutaneously in the back skin of C57BL/g5 mice when all follicles were in telogen. Endogenous SP skin concentrations and the activity of a SP-degrading enzyme, neutral endopeptidase (NEP), during the hair cycle were determined using high-performance-liquid-chromatography-controlled immunoassay for SP levels and fluorometry for NEP levels. Both capsaicin and SP induced significant hair growth (anagen) as well as substantial mast cell degranulation. Endogenous SP skin concentrations showed significant hair-cycle-dependent fluctuations, independent of NEP,

suggesting that SP may play a role in the neural control of hair growth [25, 37].

5.3.2 Calcitonin Gene Related Peptide

Calcitonin gene related peptide also has several functions and, when released from cutaneous nerve endings, it causes vasodilatation of blood vessels. In addition, CGRP inhibits Langerhans cell presentation, blocks the action of some inflammatory mediators, and can inhibit mitogen-stimulated T-lymphocyte proliferation. Interestingly, low levels of CGRP have been reported in patients with alopecia areata. Investigators have also documented an exaggerated vasodilatory response to local injection of CGRP [16, 26].

5.3.3 Neurotrophins

Neurotrophins are a family of structurally and functionally related polypeptides that may also play a role in hair diseases [7]. There are four major neurotrophin members.
These are:

- Nerve growth factor
- Brain-derived neurotrophic factor
- Neurotrophin-3
- Neurotrophin-4

The tropomyosin-related kinase (Trk) family of high-affinity transmembrane receptors binds neurotrophins. Each of the neurotrophins has a specific role in regulating different classes of functionally identified sensory neurons.

Interestingly, alterations in nerve fiber remodeling and sprouting, as well as in neurotrophin and receptor expression have been described during the murine hair cycle [5, 6, 26].

5.4 Nerves, Blood Vessels, and Lymphatic Capillares

Autonomic regulation of cutaneous blood vessels is complex, involving both somatic and autonomic innervation as well as independent local control, frequently mediated by endothelial cell nitric oxide and endothelin [8]. Most dermal vessels are densely innervated by thin unmyelinated fibers. Neuropeptide-Y-positive nerve fibers are usually found in the walls of arteries, arterioles and veins. Also, CGRP, vasoactive intestinal peptide, neurokinin A as well as SP have been found in vascular walls.

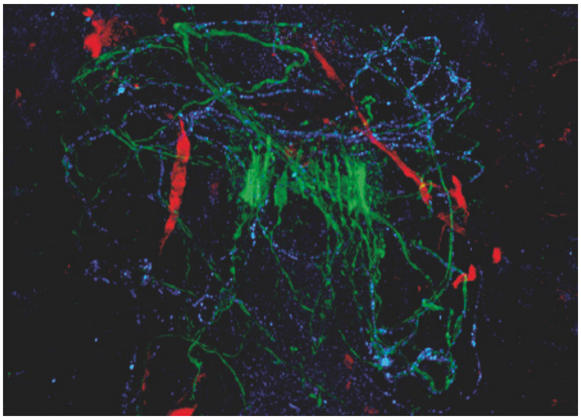


Fig. 5.3 Laser scanning confocal image of miniaturized human alopecia areata scalp hair follicle. PGP9.5 immunoreactive nerves (*green*), CGRP immunoreactivity (*blue*), and vasculature stained with *Ulex europeaous* FITC (*red*) captured with laser scanning confocal microscopy (100 × magnification)

Endothelial cells of lymphatic capillaries have many properties in common with the endothelium of blood vessels yet they also have distinct structural characteristics reflecting their specific functions [2, 28]. The lymphatic vasculature is an entry point for leukocytes and tumor cells and its close approximation to the hair follicle places lymphatic capillaries in the right place to be involved in the skin immune response (Fig. 5.3) [23].

5.5 Experimental Techniques

5.5.1 Alopecia Areata Mouse Model/ Other Animal Models

The development of mouse mutants with functional deletion or overexpression of genes coding for neurotrophins, neuropeptides or their receptors or for proteins related to nerve sprouting has given investigators significant tools with which to study piloneural interactions [34]. This is particularly true in murine model systems where follicle cycling can be synchronized. One of the most popular models is the C3H/HeJ mouse, a model for alopecia areata.

5.5.2 Hair Follicle Stem Cells and Regenerative Medicine

The hair follicle stem cell area is an abundant, easily accessible source of actively growing pluripotent adult

stem cells. These cells can differentiate into neurons, glia, keratinocytes, smooth muscle cells, and melanocytes in vitro. In in vivo studies nestin-driven green fluorescent protein (GFP) stem cells have been found to differentiate into blood vessels and neural tissue after transplantation into the subcutis of nude mice [1]. Most interesting has been the observation that hair follicle stem cells implanted into the gap region of a severed sciatic or tibial nerve greatly enhance the rate of nerve regeneration and the restoration of nerve function [15]. The results of these studies indicate that hair follicle stem cells may provide an important, accessible, autologous source of adult stem cells for regenerative medicine.

5.5.3 Topical Capsaicin

It has been suggested that cutaneous innervation is altered in alopecia areata; therefore, investigators have examined the effect of capsaicin applied topically in this disease. Capsaicin has also been reported to help one-half of the patients participating in a small treatment study of 21 Turkish patients with alopecia areata. We have reported increased expression of SP and CGRP in the perifollicular stockade region in scalp biopsy specimens taken from two patients with extensive alopecia areata who applied Zostrix HP, 0.075% q.i.d. for 21 days. We also found in post-treatment biopsy specimens swollen axons with adjacent SP-staining granules in the stockade region. Our patients also continued to report a "burning pain" sensation throughout the 21-day study. This was an unexpected adverse experience, as current dogma is that epidermal nerves "disappear" with daily capsaicin applications [3].

In another study, two patients with long-standing extensive alopecia areata were asked to apply 0.075% capsaicin to a defined area on the parietal scalp twice a day for 180 days. Two 4-mm scalp biopsy samples were taken at baseline and treatment days 21, 90, and 180. Eight biopsy specimens from each participant were fixed, processed, and prepared for confocal microscopic examination using antibodies to pan-neuronal protein gene product 9.5 (PGP 9.5), SP, CGRP, as well as the FITC-labeled lectin *Ulex europaeus* I agglutinin. Data sets were collected and three-dimensional views of nerves, neuropeptides, and vasculature captured.

After 180 days of capsaicin therapy, both patients had some vellus hair regrowth and interestingly still reported burning scalp symptoms. Examination of the 180-day scalp biopsy specimens revealed PGP-9.5-immunoreactive (ir) epidermal nerve fibers. In the mid and lower regions of miniaturized follicles, PGP 9.5-ir perifollicular nerves appeared fragmented and, in contrast to the findings seen in the initial 21-day study, no stockades, swollen axons, or SP-ir granules were detected. Whether these stockades "disappeared" or were never prominent in the first place in these individuals remains to be ascertained [17].

These results suggest that affected scalp of patients with extensive alopecia areata may respond differently to topical capsaicin, further supporting the hypothesis that the peripheral nervous system is abnormal in patients with this disease. The presence of immunoreactive epidermal fibers in the 180-day specimens was unexpected and remains to be explained in the context of current dogma. As products evolve that have neurotrophic effects on the skin, their use should be considered in this complex disease.

In summary, it appears that the persistent tingling in both patients, exacerbated by heat in patient no. 1, may be related to abnormal function of the capsaicin receptor, VR1.

5.5.4 Botulinum Toxin A

Botulinum A toxin (botox) has recently been reported as beneficial to a patient experiencing cephalalgic alopecia areata [11]. The authors postulated that the hair loss was initiated and sustained by recurrent activation of the trigeminal and upper cervical branches innervating hair follicles. They proposed that the use of botox disables the synapse between the primary afferent and the second-order neurons within the trigeminal nucleus caudals and the dorsal horn of the upper cervical spine, and in this way halts the aberrant neural activation. Once the effect of botox disappeared, the pain and hair loss both returned. This hypothesis remains to be tested but the observations support the theory that "nerves" play a role in alopecia areata [16].

5.5.5 Topical Neurotrophic Agents

Topical application of the neuroimmunophilin ligand FK506 is associated with hair growth in C57BL/6J telogen mice and in two animal models of alopecia areata: the C3H/HeJ mouse and the Dundee Experimental Bald Rat [20].

FK506 binds to FK Binding Protein-12 (FKBP-12), a cytosolic protein found in both the central and peripheral nervous systems as well as in the immune system. FKBPs play multiple roles in the nervous system and various immunophilin ligands elicit neuroprotective and neurotrophic effects. The small-molecule, synthetic FKBP immunophilin ligands GPI-1046, GPI-1485, and GPI-1511 (Gliancol Inc., New York, NY, USA) have been shown to enhance neurite outgrowth in vitro and to stimulate sprouting following partial deafferentation in numerous in vivo models of neurodegenerative dis-

eases [12, 37]. Work in our laboratory has revealed that topically applied GPI-1046 and GPI-1511 will alter the hair growth cycle of the C57BL/6J mouse and induce changes in cutaneous innervation [17]. Several in vivo and in vitro studies indicate that immunophilins may play a role in assembling and modulating multi-component protein complexes [33]. Likewise the neurotrophic effects have been shown to be mediated by SCIP, a transcription factor that regulates Schwann cell gene transcription. SCIP is upregulated by the neuroimmunophilin ligand JNJ460 in a dorsal root ganglion model [4]. Work continues on the effects of these neurotrophic agents on the alopecia areata mouse model.

5.5.6 Neurometer

It is now possible to assess nerve function in conjunction with the study of cutaneous nerves. The Neurometer CPT (Neurotron, Baltimore, Md., USA) is a device that was approved by the Food and Drug Administration in the United States in 1986. It measures current perception thresholds by utilizing a minimum intensity of transcutaneous constant-current electrical stimulus needed to evoke a sensation. Data can be obtained using three neuroselective sinusoid waveform frequencies, 5 Hz, 250 Hz, and 2000 Hz, and information is obtained using an automated double-blind methodology. Current perception thresholds can be assessed for A-beta fibers (2000 Hz), A-delta fibers (250 Hz), and C fibers (5 Hz).

Recently this device was used to study nerve function in alopecia areata subjects and normal control subjects. Sensory nerve conduction threshold was examined in C2, C7, and trigeminal V1 dermatomes [10]. Peripheral nerve function was found to be altered in affected scalp skin in contrast to no statistically significant differences found between patients and controls in the V1 dermatome. Additional studies are needed to confirm the observation that nerve function in the scalp of alopecia areata patients is abnormal. The use of the device can also be extended to other hair or scalp diseases associated with dysesthesia.

5.6 Clinical Relevance

Patients experiencing the common hair disease androgenetic alopecia frequently ask if the blood supply to their hair follicles has been compromised. They are told that no, this is a genetic disease that is androgen mediated. Yet, changes in hair follicle vasculature have been observed for decades both with the normal cycle and in hair diseases such as androgenetic alopecia [20, 32]. With new tools such as confocal microscopy, new immunohistochemical techniques, and mouse models, we have the opportunity to ascertain whether the vascular changes that occur in the pilosebaceous unit are primary or secondary [18].

Alopecia areata, a common immune-mediated hair disease, has been associated with “stress” [24]. Yet, experimental evidence to support this hypothesis is lacking. With the development of a mouse model for this disease and the availability of antibodies directed toward nerves, neuropeptides and their receptors, investigators now have the opportunity to design experiments to examine the role of nerves in alopecia areata. Concurrently, the use of electrodiagnostic equipment that noninvasively measures the current-perception threshold (Neurotron) permits the study of nerve function in the clinic. Identification and understanding of nerve, neuropeptide, and receptor function in alopecia areata will lead to improved understanding of the pathophysiology of this hair disease and may lead to improved therapy (Fig. 5.4). The successful use of botulinum toxin in a patient with scalp pain and alopecia areata supports the concept that modification of perifollicular nerves and nerve function may be beneficial to some patients with this disease. The observation that lymphatic vessels are closely aligned with the hair follicle vasculature prompts the study of interactions between the lymphatic, vascular, and nervous systems (Fig. 5.4).

5.7 Outlook – Future Developments

The potential involvement of neuropeptides, neurotrophins, and their receptors in hair diseases means that it may be possible in the future to include modulation of neurotrophin signaling or neuropeptide expression in the treatsments of hair diseases [7]. Agonists/antagonists may be developed as possible new treatments. The interactions between endothelial cells, nerves, and the lymphatic microvasculature deserve further study and may also lead to new interventions in the management of hair diseases.

The observation that botulinum toxin A may be beneficial by potentially suppressing antigen presentation, and the immune reactivity of neuropeptides such as CGPR and SP resulting in induction of hair growth in alopecia areata warrants further study. The clinical efficacy of this approach should also be examined in research trials. The opportunity to use topical neurotrophic agents in various alopecia disorders is another exciting development.

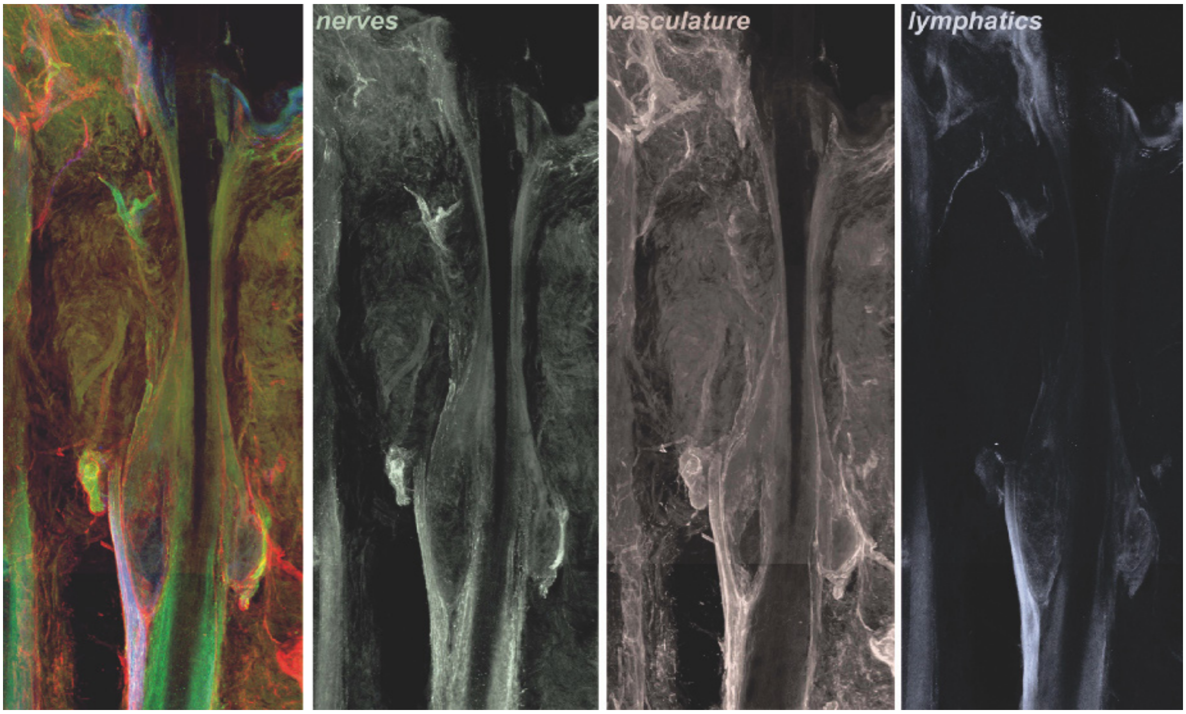


Fig. 5.4 Montage of three fields of view of confocal *z*-stack images of human scalp hair follicle immunostained with pan-neuronal marker PGP9.5 (*green*), vascular marker *Ulex-europeaous*-FITC (*red*) and lymphatic marker LYVE1 (*blue*) (100× magnification)

Summary for the Clinician

The innervation and vasculature of animal and human hair follicles are complex [21, 22]. Though this complexity has been recognized for decades, it has only recently become possible to use new technologies and animal models to study the functional roles of nerves, neuropeptides, neurotrophins and their receptors, as well as the vascular and lymphatic endothelial systems. This knowledge is being translated to the clinic; for example, the proposed study of botulinum toxin A in the management of alopecia areata. Lastly, the opportunity to use hair follicle stem cells in treating nerve injuries is very exciting.

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Chapter 6

Molecular Genetics of Human Hair Diseases

6

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Synonyms

clinical genetics, genetic hair disorders, congenital alopecia

Key Features

- Eda-A1/Edar/Edaradd/NF-κB is a key signaling pathway for hair follicle morphogenesis.
- Hairless is a critical transcription factor to control the catagen phase of the hair cycle.
- FOXN1 is involved in regulating the expression of hair keratin genes.
- Switching of two classical cadherin members in the hair follicle placode is an important event for hair follicle development.
- EEM syndrome (ectodermal dysplasia, ectrodactyly, macular dystrophy), Naxos disease (palmoplantar keratoderma with arrhythmogenic right ventricular cardiomyopathy and woolly hair) and Clouston syndrome (hidrotic ectodermal dysplasia) are molecularly well characterized.
- Desmosomal components maintain hair follicle structure and differentiation.
- Involvement of gap junction proteins in hair diseases is reported.
- LIPH (membrane-associated phosphatidic acid-selective phospholipase A1 alpha) and P2RY5 are new candidate genes for congenital hair disorders.

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6.1 Introduction

The development of the hair follicle occurs during embryogenesis. In this process, ectoderm and mesenchyme interact closely and produce a series of reciprocal signals to form a mature hair follicle [79]. Once the hair follicle is generated, it displays dynamic cell kinetics, as indicated by the hair cycle, throughout postnatal life (Chap. 1). During this cycle, hairs grow in the anagen phase, stop their growth in the catagen phase, and rest in the telogen phase as club hairs in the regressed hair follicle [101]. Among the skin appendages, the hair follicle has the most complicated structure, composed of several distinct cell layers (Fig. 6.1). The anagen hair shaft has a common structural organization, in which a multicellular cortex is encased in a cuticular layer of flattened cells, often with a medulla layer centrally placed in the cortex. The hair is surrounded and supported by the inner root sheath (IRS), companion layer, and outer root sheath (ORS). The IRS consists of three distinct layers: IRS cuticle, Huxley layer, and Henle layer. The matrix cells in the hair bulb, which originally derive from the stem cells located in the bulge region, actively proliferate and differentiate into these cell layers except for ORS [63]. Like the epidermis, the hair follicle is a highly keratinized tissue and forms a rigid structure.

Since the mid 1990s, significant advances have been made in identifying the numerous genes expressed in the hair follicle. Further studies have revealed their biological functions in hair follicle morphogenesis and/or the hair cycle [116]. Many signaling molecules, transcription factors, and structural components are differentially and sequentially expressed in the hair follicle, and generate this unique organ. In addition, we and many other groups have shown that mutations in some of these genes underlie hereditary hair disorders in humans. These findings have enabled us to directly identify the crucial genes for producing and maintaining the human hair follicle. In this chapter, we review recent progress in our understanding of the hair cycle, gene regulation, and cell-to-cell adhesion in the hair follicle. In particular, we will focus on genes that, when mutated, cause congenital hair disorders in humans.

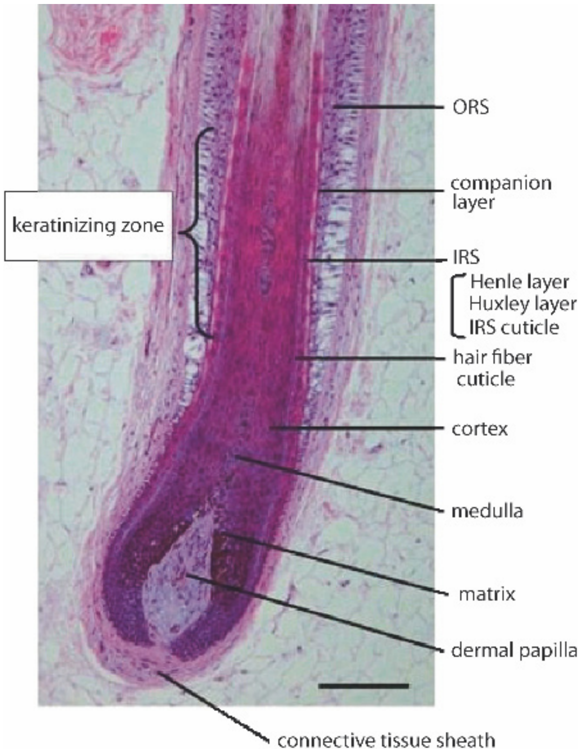


Fig. 6.1 Light micrograph of the human anagen hair follicle. (*IRS* Inner root sheath, *ORS* outer root sheath.) Hematoxylin-eosin stain. *Scale bar*: 100 µm

6.2 History

Recent advances in hair research, especially based on molecular genetics, have led to the identification and characterization of a number of genes related to hair. In addition, the involvement of these genes in human hair diseases continues to be revealed.

6.2.1 Eda-A1/Edar/Edaradd/NF-κB Signaling

6.2.1.1 Structure and Function/ Pathophysiology/Developments

Hair follicle morphogenesis begins with the formation of a placode, which is composed of groups of rearranged epidermal cells, and continues with the subsequent formation of mesenchymal condensate just beneath the placode (Fig. 6.2). The interaction between these specific structures induces downgrowth of the placode [79, 116]. The mechanisms underlying hair follicle morphogenesis have been mainly studied in mice. Normal mouse fur consists of four different hair types: (1) primary or tylotrich (guard) hairs, which are thick, straight and make up about 2%–10% of the hairs in mouse fur; (2) awl hairs, which are also thick and straight but much shorter than the tylotrich hairs; (3) auchene hairs, which are a similar length to the awl hairs, but show a single contraction; and (4) zig-zag hairs, which comprise approximately 70% of the hairs in mouse fur and display two contractions. The primary or tylotrich (guard) hair follicles are induced between embryonic days 14.5 and 16.5 (E14.5 and E16.5), whereas the non-tylotrich or secondary hair follicles, which produce the awl, auchene, and zig-zag hairs, are induced from E16.5 to postnatal day 0.5 (P0.5) [116]. During the last 10 years, the tumor necrosis factor (TNF) pathway has been shown to play a crucial role in the morphogenesis and development of the hair follicle. Since the mid 1900s, a spontaneous mouse mutant *Tabby* has been reported in the literature, which shows an X-linked recessive inheritance pattern and has a characteristic phenotype of abnormal hair, teeth, and sweat gland development. The defective gene in *Tabby* mouse, known as *ectodysplasin-A (Eda)*, was cloned in 1996 [27, 134]. The *Eda* encodes various isoforms of a type II transmembrane protein due to alternative splicing [5]. Of these variants, ectodysplasin-A1 (Eda-A1) is the longest form which shares the characteristic features of the TNF ligand superfamily. Eda-A1 is composed of an extracellular portion containing a collagenous domain and a TNF-ligand motif in its C-terminus. The Eda-A1 receptor Edar was subsequently identified as a member of the TNF receptor superfamily, since it is a type I transmembrane protein with a cysteine-rich domain in the extracellular region, and has a potential death domain in its intracellular region [39]. Before hair follicle induction, transcripts of Eda and Edar are co-localized in the simple ectodermal sheet covering the developing embryo. When hair follicle induction is initiated, *Edar* expression becomes restricted to the hair follicle placode, whereas the *Eda* shows complementary expression in the interfollicular epidermis [66, 67]. At the protein level, Eda-A1 is cleaved by a furin-like enzyme, which leads to the formation of a soluble extracellular molecule and interaction with Edar [24]. In addition, it has been shown that Edar associates with its adaptor Edaradd via its death domain, resulting in the downstream activation of NF-κB [126] (Fig. 6.3). Of the four hair types described above, the phenotype of *Tabby*

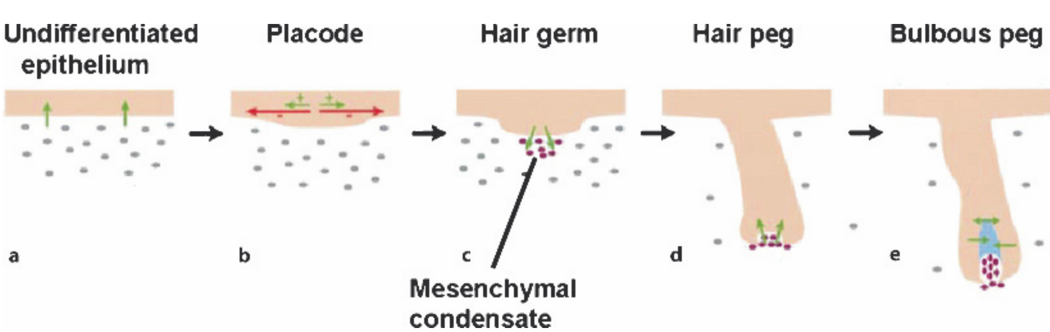


Fig. 6.2a–e Schematic drawing of hair follicle morphogenesis. In response to signals from the mesenchyme (**a**), the hair follicle placode is induced at the epithelium (**b**), which is followed by formation of mesenchymal condensate just beneath the placode (**c**). The close interactions between the epithelial and mesenchyme structures further induce the downgrowth of the placode (**d**), and differentiation of the hair follicle compartments subsequently occurs (**e**). The figure is modified from Millar [79]

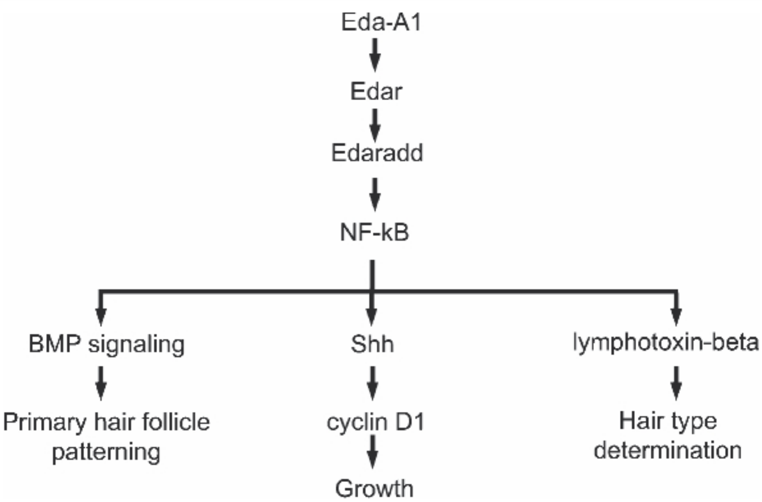


Fig. 6.3 Schematic representation of Eda-A1/Edar/Edaradd/NF-κB signaling in hair follicle morphogenesis. The figure is modified from Cui et al. [21]

lacks both guard and zig-zag hairs and has only a single atypical hair type intermediate between awl and auchene hairs [40]. It is noted that a transgene [20, 135] or recombinant protein [32] of Eda-A1 restores primary hair, but not zig-zag hair, to the *Tabby* mouse. Furthermore, Eda-A1 overexpression results in suppression of the formation of zig-zag hair in wild-type mice [90], suggesting the importance of balanced expression of Eda-A1 as well as other Eda isoforms for the formation of zig-zag hair. Nevertheless, the rescue experiments have proven that Eda/Edar signaling is essential for morphogenesis of the primary hair follicle. Recent studies have begun to disclosed the pathways downstream of NF-κB (Fig. 6.3). First, Edar has been shown to be largely involved in primary hair follicle patterning by associating with bone morphogenic protein (BMP) signaling [88]. Second, Eda-A1/Edar-mediated NF-κB activation has been demonstrated to induce Shh and cyclin D1 expression and the subsequent downgrowth of the primary hair follicle placode [117]. In addition, Eda-A1/Edar signaling has been suggested to play a role in hair type determination through the lymphotoxin-beta pathway [21].

6.2.1.2 Experimental Techniques

Three spontaneous mouse mutants (*sleek, downless,* and *crinkled*) have been known to display identical phenotypes with the *Tabby* mouse. Recent studies have shown that *Sleek* and *downless* have, respectively, autosomal dominant and autosomal recessive mutations in the *Edar* gene [39], and *crinkled* possesses an autosomal recessive mutation in the *Edaradd* gene [40]. These mouse mutants have been used to elucidate the involvement of Eda-A1/Edar signaling in ectodermal morphogenesis.

6.2.1.3 Clinical Relevance

Hypohidrotic ectodermal dysplasia (HED) is a congenital disorder characterized by the absence or hypoplasia of hair, teeth, and eccrine sweat glands, which shows a similar phenotype with *Tabby/Sleek/downless/crinkled* mice. HED usually shows an X-linked recessive inheritance pattern (Online Mendelian Inheritance in Man [OMIM] 305100) while in a small fraction HED is inherited as an autosomal dominant (OMIM 129490) or autosomal recessive trait (OMIM 224900). A candidate gene for X-linked HED, the *EDA* gene, was cloned on the human X chromosome [5, 54, 82]. Subsequently, the *EDAR* gene was identified on chromosome 2q11-q13 and proven to be responsible for autosomal dominant and autosomal recessive HED [83]. In addition, together with identification of the mouse *Edaradd* gene, the human *EDARADD* gene has been cloned on chromosome 1q42.2-q43 and a homozygous nonsense mutation has been detected in a family with HED showing an autosomal recessive trait [40].

6.3 Hairless

6.3.1 Structure and Function/Pathophysiology/Developments

A number of mutations causing generalized hair loss occur in laboratory mice. Among these, the hairless mouse (*hr*) has been known as a model for alopecia since 1926 [13]. *hr* mutants show normal development of hair follicles, however all hairs are shed soon after birth and new hairs never re-grow. Histologically, the most character-

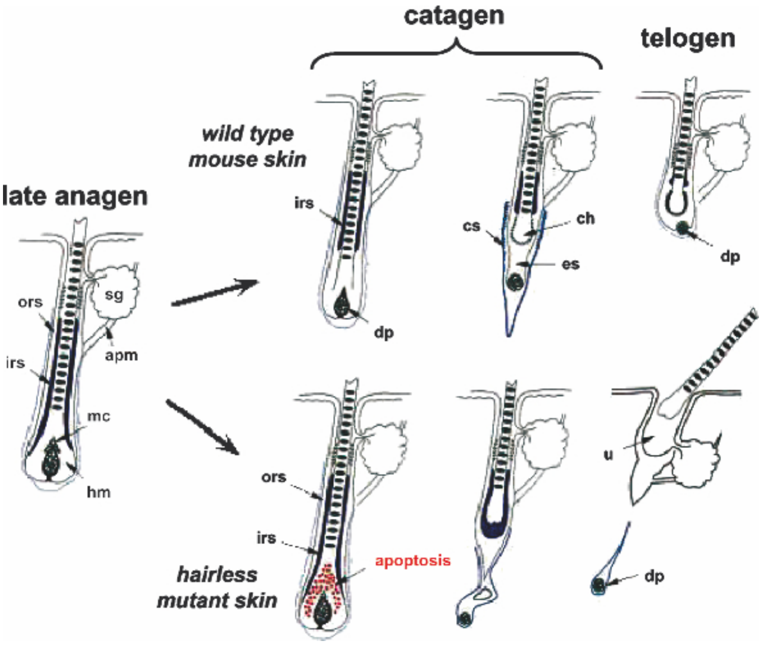


Fig. 6.4 Schematic representation of abnormal catagen phase in hairless mutant skin as compared with wild-type skin. During the catagen phase of wild-type skin, the hair follicle regresses together with dermal papilla (*upper series*). By contrast, in hairless mutant skin, the hair follicle undergoes in aberrant apoptosis and abnormally regresses, leaving behind the dermal papilla in the subcutis (*lower series*). (*apm* Arrector pili muscle, *ch* club hair, *cs* connective tissue sheath, *dp* dermal papilla, *es* epithelial strand, *hm* hair matrix, *irs* inner root sheath, *mc* melanocytes, *ors* outer root sheath, *sg* sebaceous gland, *u* utricle.) The figure is modified from Irvine and Christiano [46]

istic feature of *hr* mouse is abnormal degeneration of the hair follicle, leaving behind the dermal papilla in the subcutis in the first catagen phase [98]. During normal catagen, apoptosis occurs in a carefully timed sequence in the different compartments of the hair follicle, and the hair follicle epithelium regresses, remaining in close touch with the dermal papilla (Fig. 6.4). In the catagen phase of the *hr* mouse, however, the proximal hair bulb shows premature, ectopic, and excessive apoptosis. This burst of programmed epithelial cell death leads to disruption of the contact between the hair follicle epithelium and the dermal papilla. In addition, the ORS shows striking atrophy and fails to undergo trichilemmal keratinization. In the end, characteristic utriculi and dermal cysts are formed in the dermis. The *hairless gene (hr)*, the causative gene for the *hr* mouse, encodes a putative single zinc-finger transcription factor. In situ hybridization studies have demonstrated that, in normal catagen hair follicles, *hr* is expressed strongly in the zone of developing club hair and in epithelial cells adjacent to dermal papilla [99]. These data indicate that *hr* regulates the catagen phase so as to maintain the hair follicle's capacity to start the next hair cycle. *hr* mutants also display immunological skin dysfunction, elevated sensitivity to ultraviolet light and chemically induced skin carcinogenesis [74, 87] and a unique susceptibility to dioxin skin toxicity [96]. Although the importance of hr in the skin is evident, its biochemical function remains largely unknown. So far, hr has been shown to function as a transcriptional co-repressor for the thyroid hormone receptor (TR) [103, 140] and vitamin D receptor (VDR) [43]. In particular, two independent regions of hr have been identified as interaction sites with TR [103]. Furthermore, recent studies have demonstrated that hr binds to VDR and represses both basal and ligand-dependent VDR-mediated transactivation [127]. Interestingly, it has also been shown that the effects of the VDR on the hair follicle are ligand independent, and that hr co-localizes with VDR in the nucleus of the hair follicle cells [127, 152]. Taken together, repression of basal transcription by an hr–VDR complex may play an essential role in maintaining the hair cycle, even though the target genes are not yet identified.

6.3.2 Experimental Techniques

It is known that the mutation in the *hr* mouse is caused by spontaneous integration of a modified polytropic retrovirus into intron 6 of the *hr* gene, which results in abnormal splicing and only about 5% normal *hr* transcripts present in *hr* mouse [14]. In addition, the rhino mouse (hr^{rh}), which exhibits a similar hair phenotype to the *hr* mouse, possesses homozygous nonsense mutations in the *hr* gene [2, 97].

6.3.3 Clinical Relevance

The human *hairless* gene (*HR*) was cloned on chromosome 8q21-22, in a region syntenic with the mouse *hr* locus on chromosome 14q [1, 16]. The amino acid se-

quence alignment of human and mouse *hr* shows high homology (84%), suggesting a high conservation and functional significance of hr. Indeed, mutations in both alleles of the human *HR* gene cause a severe congenital hair disease, atrichia with papular lesions (APL; OMIM 209500) [1, 16]. The term atrichia is reserved for the most dramatic and severe forms of hair loss, in particular those characterized by an absence of hair follicles [158]. Patients with APL display quite a similar phenotype to the *hr* mouse. It is characterized by early onset of complete hair loss (atrichia), which is followed by papular eruptions due to the formation of a dermal cyst after an abnormal first catagen phase. In addition, atrichia with papules also occurs in the clinical setting of vitamin-D-dependent rickets type IIA (VDDRIIA; OMIM 277440), which is caused by recessively inherited mutations in the VDR gene [44]. In spite of the distinct genetic basis for both forms of atrichia the clinical findings are strikingly similar, which further suggests a functional relationship between HR and VDR [158].

6.4 FOXN1 and Hair Keratins

6.4.1 Structure and Function/ Pathophysiology/Developments

The hair fiber is a highly keratinized tissue that is the end-product formed by the hair follicle. The major structural components of hair are hair keratins, which form the intermediate filaments in trichocytes and play a crucial role in hair fiber keratinization. To date, 11 type I and 6 type II hair keratin genes have been identified in humans [108, 109]. These are expressed sequentially and differentially in compartments of the hair fiber [64, 65] and nail [102]. Recently, more of the genes that control the expression of hair keratins have been defined, including *Foxn1* (*FOXN1* in humans), which was the first to be found using linkage analysis and an autosomal recessive mouse mutant, *"nude."* It was originally designated *whn* (*winged-helix-nude*) or *hfh11* (*hepatocyte nuclear factor 3/forkhead homolog 11*), but was later renamed *Foxn1* (*Forkhead box n1*), according to the revised nomenclature. *Foxn1* encodes a member of the forked/winged-helix domain family of transcription factors [91]. In the anagen hair follicle, Foxn1 is strongly expressed in the upper matrix, precortex, and cortex of the hair fiber [68], suggesting that Foxn1 might activate genes essential for hair fiber differentiation. Several lines of evidence support this suggestion, especially about the involvement of Foxn1 in the expression of some hair keratin genes. First, it was shown that transcripts of a mouse type I hair keratin gene, *mHa3* (*Krt33b* in the recently proposed nomenclature of keratins [119]), are completely absent in pelage hair follicles of nude mice [75]. Then, all hair keratin genes except for *mHa5* (*Krt35*) were shown to be downregulated in *nude* mice [114]. Furthermore, overexpression of Foxn1 in human HeLa cells markedly activated the expression of human type I hair keratin genes *KRTHA3B* (*KRT33B*), and the type II hair keratin genes *KRTHB1* (*KRT81*), *KRTHB3* (*KRT83*), *KRTHB5* (*KRT85*) and *KRTHB6* (*KRT86*) [114]. These data strongly indicate that Foxn1 is a regulator of some hair keratin genes, but direct evidence that Foxn1 binds to the promoter of hair keratin genes remains to be elucidated. More recently, Johns et al. [51] have shown that nude mice exhibit a marked deficiency of septulate hairs with multiple columns of medulla cells, which suggests that Foxn1 is required for proper assembly of the hair fiber medulla even though its expression is undetectable in the medulla cells. The study also showed the Foxn1-dependent expression of desmocollin 2 (Dsc2), a member of the desmosomal cadherin gene family, in junctions between the hair fiber cortex and the medulla, indicating that Foxn1 might promote the expression of a signal in the cortex to induce medulla cells to upregulate Dsc2-expression.

6.4.2 Experimental Techniques

It is known that *nude* mice have disrupted postnatal hair growth and show severe T-cell immunodeficiency due to thymic aplasia [28]. Hairs of *nude* mice are very thin and easily form coils within the hair follicle, indicating a defect in hair fiber keratinization. Also, *nude* mice possess homozygous mutant *Foxn1* alleles, which result in the truncated protein lacking both the DNA-binding and transcriptional activation domains [91].

6.4.3 Clinical Relevance

In humans, the *FOXN1* gene was cloned on chromosome 17 [118], and homozygous nonsense mutations in this gene were subsequently identified in patients affected with T-cell immunodeficiency, congenital alopecia, and nail dystrophy (OMIM 601705), which represents the human counterpart of the nude mouse phenotype [30].

Mutations in three type II hair keratin genes, *KRTHB1* (*KRT81*), *KRTHB6* (*KRT86*) [150], and *KRTHB3* (*KRT83*) [143], have been shown to cause an autosomal-dominant hypotrichosis, known as monilethrix (OMIM 158000). The disease is characterized by a particular hair shaft anomaly called a moniliform hair (Fig. 6.5). All three hair keratins are predominantly expressed in the keratinizing zone of the hair fiber cortex, where hair fiber keratinization actively occurs [65].

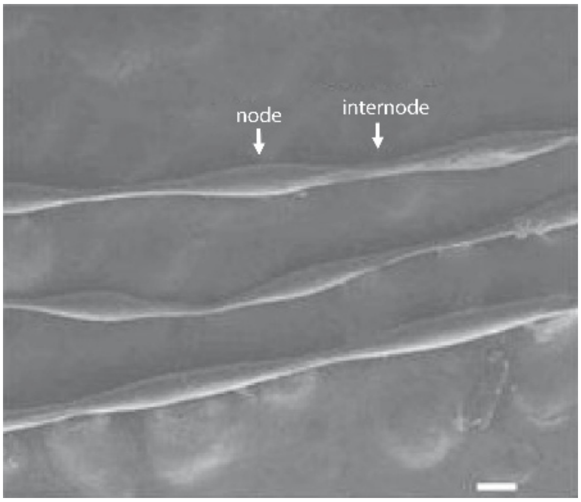


Fig. 6.5 Scanning electron microscopy of typical moniliform hair. The thickness of moniliform hair is inconsistent, which results in the formation of nodes and internodes. The moniliform hair often breaks at the internodes. *Scale bar:* 100 µm

6.5 Classical Cadherins

6.5.1 Structure and Function/ Pathophysiology/Developments

Adhesions junctions (AJs) are one of the major intercellular junctions that connect the actin filament to sites of cadherin-based adhesion. The classical cadherins form the transmembrane core of AJs in many tissues. Their intracellular regions link them with β-catenin and consequently to α-catenin, vinculin, and the actin filament network [3, 38] (Fig. 6.6). The classical cadherins are known to be involved in many biological processes, such as cell recognition, cell signaling, morphogenesis, and tumor development [35]. Among the classical cadherins, E-cadherin (epithelial cadherin) and P-cadherin (placental) are the main ones expressed in the epidermis and hair follicle [89]. Recently, their involvement in hair follicle morphogenesis was highlighted. In the epidermis, E-cadherin is abundantly expressed in the basal and suprabasal layers, and P-cadherin is expressed only weakly in the basal layer. However, upon formation of the hair follicle placode, the expression of E-cadherin is markedly downregulated. By contrast, P-cadherin becomes much more strongly expressed in the placode than in the interfollicular epidermis [42] (Fig. 6.7). This predominant expression of P-cadherin continues to be detected in the proximal portion of the hair germ, hair peg, bulbous hair, and even mature hair follicle [42].

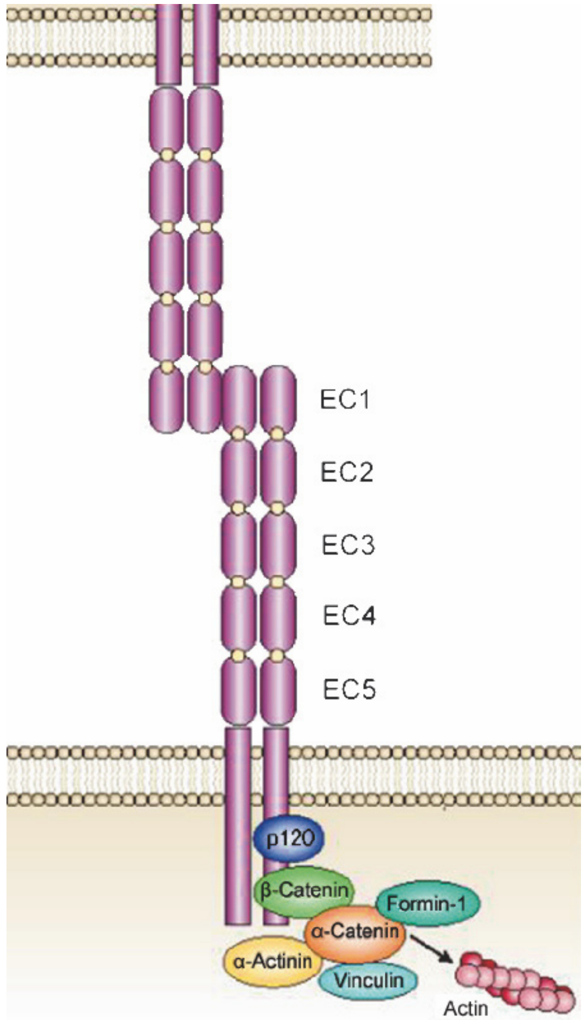


Fig. 6.6 Schematic representation of the classical cadherin–catenin complex to form adhesions junctions. The cadherin members possess five extracellular cadherin domains (*EC1–5*), which are important for cell-to-cell adhesion. The intracellular regions of classical cadherins interact with the so-called catenin complex, which anchors the actin filaments. The figure is modified from Gumbiner [38]

Recently, Jamora et al. [48] showed that two distinct signaling pathways contribute to the downregulation of E-cadherin: (1) a winged (Wnt) protein to stabilize β-catenin, and (2) Noggin, a bone morphogenic protein (BMP) inhibitor, to produce lymphoid enhancer factor-1 (Lef-1) [48]. In addition, they demonstrated that transgenic mice overexpressing E-cadherin under the K14 promoter have a paucity of hair follicles due to failure of E-cadherin downregulation. It is evident that “the cadherin switch” plays a crucial role in changing cell-to-cell contacts in the hair follicle placode. To date,

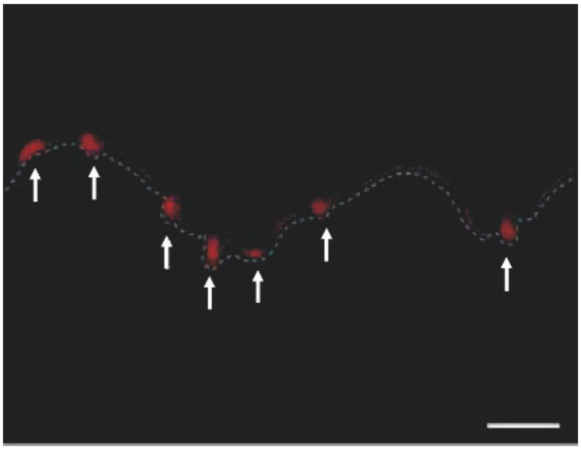


Fig. 6.7 Expression of P-cadherin in the back skin of the E15.5 mouse embryo. Note that P-cadherin protein is strongly expressed at the hair follicle placode (*white arrow*). *Scale bar*: 100 µm

however, molecular mechanisms for the upregulation of P-cadherin in the placode remain unknown.

6.5.2 Experimental Techniques

The P-cadherin knockout mouse was produced in 1997 [104]. Surprisingly, it showed only an abnormal differentiation of the mammary gland, while any other anomalies, including hair defects, were not described.

6.5.3 Clinical Relevance

Recently, recessively inherited mutations in the *CDH3* gene encoding P-cadherin have been shown to cause two congenital diseases in humans. First, mutations in the *CDH3* gene were identified in families with hypotrichosis with juvenile macular dystrophy (HJMD; OMIM 601553), which is characterized by sparse hair and early blindness due to macular dystrophy of the retina [133]. Later, Kjaer et al. [56] reported that EEM syndrome (ectodermal dysplasia, ectrodactyly, and macular dystrophy; OMIM 225280) is also caused by mutations in the *CDH3* gene [56]. Affected individuals with EEM syndrome show a common hair and eye phenotype with HJMD. However, they also exhibit an additional split hand/foot malformation. The data strongly suggest involvement of P-cadherin in the development of not only the hair and eyes but also the limbs in humans.

To date, the genes which control the expression of P-cadherin remain largely unknown. It is noteworthy that mutations in p63 gene also show sparse hair and split foot/hand malformations in both human [15] and mouse [80, 155]. p63 is a transcription factor expressed primarily in epithelia and is known to regulate the expression of many genes [154]. We recently demonstrated that the expression of P-cadherin and p63 overlaps not only in the hair follicle placode, but also in the developing limb bud of the mouse embryo [123]. Furthermore, we showed that P-cadherin is a p63 target gene and plays a crucial role in the developing hair follicle and limb bud in humans [123]. However, the reason for the different phenotype between P-cadherin-knockout mouse and P-cadherin-mutant humans is unknown.

6.6 Desmosomal Cadherins

6.6.1 Structure and Function/ Pathophysiology/Developments

The desmosome is a structure critical for cell-to-cell adhesion in epithelial tissues, meninges, the dendritic reticulum cells of lymph node follicles, and the myocardium [71]. One of the major structural components of the desmosome are the desmosomal cadherins, which are made up of the desmogleins (DSGs) and desmocollins (DSCs). Both DSGs and DSCs have several members and their genes are located on the same gene cluster in humans, mice, and rats [47]. The desmosomal cadherin family members are transmembranous glycoproteins involved in Ca^{2+}-mediated cell-to-cell adhesion,

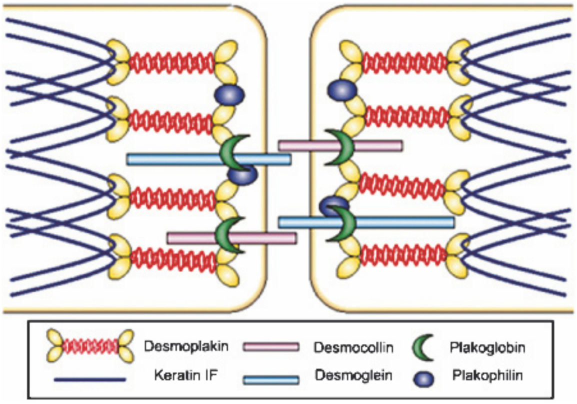


Fig. 6.8 Schematic representation of desmosome. Like classical cadherins, desmosomal cadherins bind to those of adjacent cells via their extracellular domains. The intracellular region of the desmosomal cadherins connects with desmosomal plaque proteins and anchor keratin intermediate filaments (*IF*). With permission from Fuchs and Raghavan, [31]

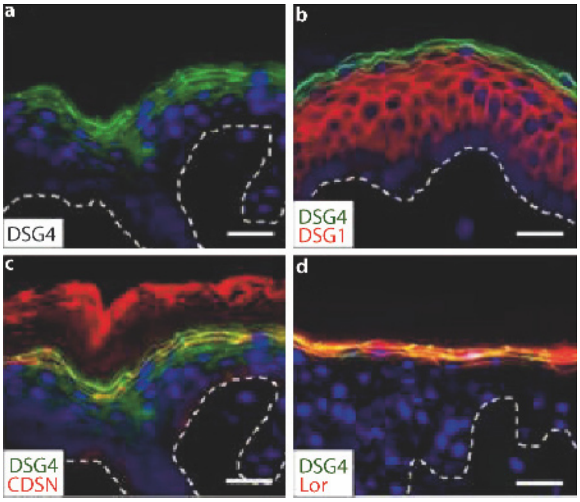


Fig. 6.9a–d Expression of desmoglein 4 in the human epidermis. **a** The expression of desmoglein 4 (*DSG4*) is observed in a highly differentiated part of the epidermis. **b** Its expression level in the uppermost living layer of the epidermis is higher than that of DSG1. In addition, DSG4 co-localizes with other differentiation markers such as corneodesmosin (*CDSN*) (**c**) and loricrin (*Lor*) (**d**). *Scale bars:* 60 µm. With permission from Bazzi et al. 2006 [7]

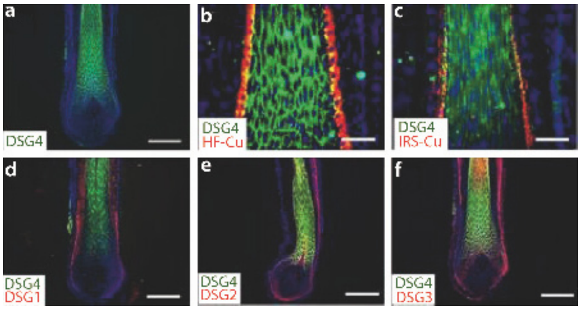


Fig. 6.10a–f Expression of desmoglein 4 (*DSG4*) in the human hair follicle. **a** DSG4 is expressed in highly differentiated portions of the hair shaft, especially precortex and cortex regions. Double immunostainings with hair-specific keratin antibodies have demonstrated that DSG4 is expressed in hair fiber cuticle (*HF-Cu)* (**b**) and inner root sheath cuticle (IRS-Cu) (**c**) as well. As compared with DSG1 (**d**), DSG2 (**e**), and DSG3 (**f**), DSG4 is predominantly expressed in the hair fiber cortex including the keratinizing zone. *Scale bars:* 400 µm (a, d, e, f), 70 µm (b, c). With permission of Bazzi et al. 2006 [7]

and connect with each other via their extracellular domains. Detailed observation of desmosomes with electron microscopy has demonstrated the presence of an electron-dense plaque, called the "desmosomal plaque," in the cytoplasm parallel to the junctional region [71]. Desmosomal plaque has three constituents: plakophilin (PKP), junctional plakoglobin (PG), and desmoplakin (DSP). These proteins function as linker molecules and anchor the intermediate filaments at the cell membrane (Fig. 6.8). As such, the desmosomes connect cells to one another, and maintain tissue integrity.

There are four known DSG (DSG1–DSG4) and three DSC (DSC1-DSC3) types in humans, and they have specific temporal and spatial expression patterns during epithelial differentiation. In the epidermis, DSG2 and DSC2 are expressed in the basal layer; DSG3 and DSC3 are expressed basally and suprabasally with decreasing expression in the suprabasal layers; finally, DSG1 and DSC1 are expressed highly in the suprabasal layers [36, 156]. In addition, expression of the DSG members in the hair follicle has been characterized in detail [151]. DSG2 and DSG3 are expressed in the lower ORS as well as the matrix and precortex, while DSG1 is expressed in the IRS and suprabasal layers of the ORS. DSG3 is also expressed in the medulla of the hair shaft. It has been shown that transgenic mice with homozygous nonsense mutations in the desmoglein 3 gene (*bal* mice) show striking hair loss [36], which emphasizes the possibility that mutations in DSGs may cause congenital hair disorders in humans as well, even though no human counterpart of the *bal* phenotype has yet been identified.

Recently, a fourth member of the DSG family, desmoglein 4, was cloned in humans and mice [57, 147], and the precise expression analysis of DSG4 in human skin and hair follicle has been delineated [7]. In the epidermis, DSG4 expression begins at the upper spinous layer and reaches its highest levels in the granular layer just beneath the cornified layer (Fig. 6.9a, b). Its expression overlaps that of some differentiation markers such as corneodesmosin (Fig. 6.9c) and loricrin (Fig. 6.9d). Furthermore, in vitro studies have demonstrated that DSG4 is expressed in the highest differentiation state of epidermal keratinocytes. Likewise, DSG4 expression is detected mainly in the highly differentiated state of the hair shaft, especially the precortex and cortex (Fig. 6.10a). Furthermore, double immunostainings with anti-DSG4 and anti-hair-specific keratin antibodies have confirmed the expression of DSG4 in the lower hair fiber cuticle (Fig. 6.10b), and the upper IRS cuticle (Fig. 6.10c) as well. Compared with other DSG subtypes, DSG4 is primarily expressed at high levels in the hair fiber cortex, including the keratinizing zone in which hair keratins are abundantly expressed and form the strong intermediate filament network (Fig. 6.10d–f) [7].

6.6.2 Experimental Techniques

Several autosomal-recessive mouse and rat mutants have been shown to share a characteristic hair-shaft anomaly in which a broken end shows a lance-head shape, thus it is termed "lanceolate hair (*lah*)" [84, 136]. Histologically, the formation of a bulbous "bleb" in the hair shaft within the hair follicle is often observed in the *lah* animals. The mouse Dsg4 gene has been identified and homozygous mutations have been found in the Dsg4 gene of the *lah* mice [57]. Subsequently, rat Dsg4 has also been cloned [47], followed by detection of *Dsg4* mutations in the rat *lah* phenotype [6, 47, 78].

6.6.3 Clinical Relevance

Discovery of the human *DSG4* gene was achieved by linkage studies on human pedigrees with localized autosomal recessive hypotrichosis (LAH; OMIM 607903) [57]. Homozygous deletion mutations were detected in affected individuals with LAH [57]. Patients with LAH were originally found in consanguineous Pakistani families, who presented with hypotrichosis limited to the scalp, chest, arms, and legs. The eyebrows and beard are less dense than normal, and the axillary hair, pubic hair, and eyelashes are normal. Most recently, recessive mutations in the *DSG4* gene have been identified in several patients with recessively inherited monilethrix as well [113, 122, 159]. These data indicate that aberrant DSG4 proteins cause perturbations in the switch from proliferation to differentiation of trichocytes, which leads to abnormal and premature keratinization of the hair fiber, and can result in moniliform hairs as part of the phenotype in some cases.

6.7 Plakophilin 1

6.7.1 Structure and Function/ Pathophysiology/Developments

Plakophilin (PKP) is a member of the armadillo protein family, which is defined by the presence of a 42-amino-acid repeated motif termed an armadillo (arm) domain. To date, a total of four PKPs (PKP1–4) have been identified. Among these, PKP1 is a major component of desmosomes in stratifying and complex epithelia [131]. In addition, it is also expressed widely in the nuclei of many cell types [115]. Thus, PKP1 is considered to function not only as a desmosomal component but also as a signaling molecule involved in gene expression. So far, however, no interaction between PKP1 and a nuclear protein has been found. In the epidermis, PKP1 is expressed weakly in the basal layer and strongly in the spinous and granular layers, while no expression is detected in the corneal layer [81]. In the hair follicle, PKP1 is expressed preferentially in the suprabasal layers of the ORS [81]. In vitro biochemical studies have demonstrated that PKP1 can bind to keratin intermediate filaments (KIFs) as well as DSP and desmosomal cadherins [128]. In vivo, it has been suggested that PKP1 localizes closest to the plasma membrane within the desmosomal plaque and mainly interacts with DSP [93].

6.7.2 Experimental Techniques

To date, animal models for PKP1 mutations have not been established. However, patients with complete ablation of PKP1 have been identified (see Sect. 6.7.3), which provides us with a valuable resource to understand the function of PKP1.

6.7.3 Clinical Relevance

In humans, *PKP1* is the causative gene for an autosomal recessive genodermatosis, ectodermal dysplasia/skin fragility syndrome (OMIM 604536), which is characterized by cutaneous fragility and congenital ectodermal dysplasia affecting skin, hair, and nails [72]. The patient investigated was a compound heterozygote for two nonsense mutations in the *PKP1* gene. Immunohistochemical studies have shown that there was no PKP1 expression in the patient's epidermis most probably due to nonsense-mediated mRNA decay. In electron microscopic observations, aberrant cytoplasmic distribution of DSP and perinuclear aggregation of KIFs were observed, indicating that the loss of PKP1 results in the disruption of DSP distribution and the abnormal aggregation of KIFs [72]. In vitro studies using PKP1-null cells derived from patients have demonstrated that PKP1 affects the size and number of desmosomes, keratinocyte cell migration, and the calcium stability of desmosomes [132]. Furthermore, biopsy from the patient's scalp skin showed an increased number of catagen–telogen hair follicles, which suggested a disturbance in the hair cycle [8].

6.8 Plakoglobin and Desmoplakin

6.8.1 Structure and Function/ Pathophysiology/Developments

Junctional plakoglobin (PG) is the first member discovered of the armadillo family of proteins [19]. PG

associates with the cytoplasmic domain of desmosomal cadherins, and links them to desmoplakin (DSP) [36] (Fig. 6.8). In addition, PG is also able to associate with some classical cadherins such as VE-cadherin [19]. Therefore, PG can be found in both desmosomes and adhesions junctions (AJs), whereas β-catenin, the closest relative of PG, is involved in AJs only. Mice deficient in PG have been generated by targeted disruption, and demonstrate the essential role of PG in both skin and heart. The $pg^{-/-}$ mice, especially on a 129/Sv background, usually died between days 12 and 16 of embryogenesis due to severe heart defects [110]. Histologically, myocardiac desmosomes were markedly reduced in number and structurally altered. By contrast, the formation of extended AJs was observed in the myocardium of $pg^{-/-}$ mice. No skin defects were detected in $pg^{-/-}$ mice that died during early embryogenesis. Nevertheless, some mutant mice on a C57BL/6 background survived around birth and exhibited dramatic skin blistering [10]. Ultrastructural analysis of the epidermis of these mice demonstrated a reduced number of desmosomes, which led to acantholysis and cytolysis in the granular layer and the absence of the stratum corneum. Interestingly, in $pg^{-/-}$skin, β-catenin was shown to be localized to desmosomes and associated with desmoglein, indicating the possibility that β-catenin in part compensates for a lack of PG [11]. The data obtained from the PG-knockout mice indicate that PG is an essential component of desmosomes in myocardium and epidermis, a theory also supported by in vitro experiments using keratinocytes established from PG-knockout mice [157].

In addition, Teulière et al. [139] generated transgenic mice expressing, N-terminal-truncated PG in the epidermis, that lacked glycogen synthase kinase 3β phosphorylation sites to avoid degradation (transgenic line K5-ΔN122-PG). The transgenic mice showed the formation of additional hair germs, hyperplastic hair follicles, and hair-derived tumors. However, ΔN-22-PG did not induce such abnormalities when it was expressed in β-catenin-null epidermis. Therefore, it has been suggested that the expression of ΔN122-PG cannot substitute for β-catenin in its signaling functions, but would lead to the aberrant activation of β-catenin in K5-ΔN122-PG mice. Furthermore, it is noted that the expression of ΔN122-PG in β-catenin-null skin significantly increases the survival rate of mutant mice and rescues differentiation, indicating that PG may also be involved in the intracellular signaling events essential for epidermal differentiation [139].

DSP is a member of the plakin family of cytoskeletal linker proteins. The DSP gene encodes two splice variants: the longer isoform DSP I, and the shorter isoform, DSP II [37]. These isoforms share common globular N-terminal and C-terminal, but differ in the length of the central alpha-helical rod domain. The globular N-terminal domain is required for localization to the desmosome and interacts with the armadillo family members PKPs and PG [59, 60], while the globular C-terminal domain binds with intermediate filaments [58, 76]. In addition, the coiled-coiled rod domain is responsible for homodimerization [37]. DSP-knockout mice died as embryos and did not survive beyond E6.5 [33]. These embryos showed an impressive reduction in both the number and size of desmosomes. Furthermore, the organization of keratin intermediate filament (IF) networks was markedly abnormal. Thus, the analysis revealed that DSP plays critical roles both in desmosome assembly and/or stabilization and in anchoring IFs to desmosomes. More recently, Vasioukhin et al. [144] have generated an epidermis-specific DSP-knockout mouse, which enabled a further understand the function of DSP in the epidermis [144]. DSP-null skin easily peeled after mild mechanical stress. Histologically, intercellular separations were observed particularly within the basal and spinous layers of the epidermis. The epidermal desmosomes in the DSP-null skin were only slightly reduced in number and size, but they uniformly lacked intracellular plaque structure and attachment to keratin filaments, which compromised their function. Interestingly, very few AJs were seen in the basal and spinous layers of the DSP-null epidermis. In vitro, DSP-null keratinocytes possessed few desmosomes and were unable to undergo actin reorganization and membrane sealing during epithelial sheet assembly, a process that requires the formation of AJs. These data suggest an essential role of DSP in epidermal sheet formation.

6.8.2 Experimental Techniques

As described above, some knockout or transgenic mice of PG and DSP have been generated and illustrate the biological importance of these proteins.

6.8.3 Clinical Relevance

Naxos disease (OMIM 601214) is an autosomal recessive disorder characterized by arrhythmogenic right ventricular cardiomyopathy, woolly hair, and palmoplantar keratoderma. The disease was initially mapped to chromosome 17q21, in which the *plakoglobin* gene (*JUP*) is located [18]. Subsequently, homozygous mutations have been identified in the *JUP* gene of affected individuals with Naxos disease [73].

Heterozygous mutations in the *DSP* gene were shown to underlie some cases of the autosomal-dominant skin disorder striate palmoplantar keratoderma (OMIM 148700), which is characterized by linear and focal hyperkeratosis of the palms and soles [4, 140]. Later,

Norgett et al. [88] reported that recessive mutations in the C-terminal domain of DSP caused palmoplantar keratoderma with left ventricular cardiomyopathy and woolly hair (Carvajal syndrome; OMIM 605676), which is regarded as a severe variant of Naxos disease. Furthermore, Whittock et al. [149] have discovered compound heterozygosity for premature stop codon and missense mutations in patients with skin fragility, woolly hair syndrome (OMIM 607655), which is characterized by focal and diffuse palmoplantar keratoderma, hyperkeratotic plaques on the trunk and limbs, and woolly hair with varying degrees of alopecia, who later developed cardiac disease [149]. DSP mutations have been shown to underlie various phenotypes in humans. In particular, recessive DSP mutations are likely to affect the desmosomal structure of hair follicles, which leads to the woolly hair phenotype.

6.9 Corneodesmosin

6.9.1 Structure and Function/ Pathophysiology/Developments

Cohesion of the stratum corneum (SC) of the epidermis is largely dependent on modified desmosomes, known as corneodesmosomes [126]. During the transition from the granular layer to the SC, the morphology of desmosomes changes dramatically. In corneodesmosomes, the cytoplasmic plaque is not observed, and a homogeneous electron-dense plug occurs instead of the characteristic symmetrical tri-lamellar structure of the extracellular core [77]. Corneodesmosome degradation is considered to be the major event in the desquamation process [120]. The major adhesive transmembrane components of corneodesmosomes are DSG1 and DSC1. Furthermore, using monoclonal antibodies raised against plantar SC, corneodesmosin (CDSN) has been identified as an additional component of corneodesmosomes [120]. CDSN is synthesized in the upper spinous and/or lower granular layers in the form of a 52- to 56-kDa phosphorylated basic glycoprotein. It is secreted by cytoplasmic vesicles called keratinosomes into the extracellular core of desmosomes, when they are modified to corneodesmosomes [120, 125].

During the maturation of the SC, CDSN is progressively proteolysed by several serine proteases such as the stratum corneum chymotryptic enzyme and the stratum corneum tryptic enzyme [126]. The reduction in size is likely to participate in the loss of adhesivity of the SC, which leads to desquamation. Immunohistochemical studies have shown that CDSN is expressed predominantly in the IRS of the hair follicle [70]. Furthermore, transgenic mice bearing a 4.2-kb fragment of the human *CDSN* gene promoter linked to the *LacZ* gene has clearly demonstrated the expression of LacZ in the Henle and Huxley layers of the IRS [34]. IRS is keratinized earlier than the hair shaft, and degraded at the level of the isthmus. The expression of CDSN begins at the late stage of IRS keratinization and continues until degradation of the IRS. As in the epidermis, CDSN seems to be largely involved in terminal differentiation of the IRS.

6.9.2 Experimental Techniques

Although *CDSN* mutant animal models have yet to be established, recently identified human *CDSN* mutations have illustrated the essential role of CDSN in the hair follicle (see Sect. 6.9.3).

6.9.3 Clinical Relevance

Recently, the autosomal dominant hair disorder hypotrichosis simplex of the scalp (HSS; OMIM 146520) was mapped to chromosome 6p21 [9], and subsequently heterozygous nonsense mutations in the *CDSN* gene were identified in patients with HSS [70]. The disease is characterized by progressive loss of scalp hair starting in the middle of the first decade of life, with almost complete hair loss experienced by the third decade. Histologically, the IRS of the patient's hair follicle is disturbed [70]. Furthermore, aggregates of abnormal CDSN accumulate around the hair follicle as well as in the papillary dermis. It has been suggested that these aggregates are toxic to the hair follicle cells and a dominant, negative interaction between the mutant and wild-type CDSN protein might account for loss of cohesion in the IRS.

6.10 Gap Junction Proteins

6.10.1 Structure and Function/ Pathophysiology/Developments

In addition to AJs and desmosomes, intercellular communication is facilitated by clusters of gated intercellular channels in specialized membrane structures called gap junctions (GJs) [106]. GJs are composed of connexins (Cxs), a family of proteins that play a crucial role in cell-to-cell communication. All Cx members possess a common structure with four transmembrane domains, while they differ mainly by the size and nature of their C-terminal intracellular tail (Fig. 6.11). Cxs form hexamers called connexons, which directly interact with connexons from adjacent cells to form a complete intercellular gap junction channel that provides a

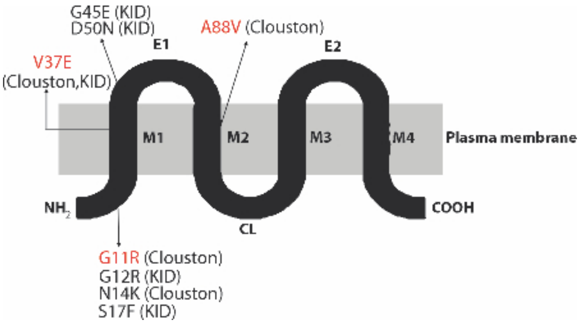


Fig. 6.11 Schematic representation of connexin protein and mutations in Cx26 and Cx30 that cause either Clouston syndrome or KID syndrome. Mutations in Cx26 and Cx30 are colored in *black* and *red*, respectively. The phenotype caused by each mutation is also indicated. (*CL* cytoplasmic loop, *E* extracellular domain, *M* transmembrane domain)

pathway for both metabolic and ionic coupling between neighboring cells, and maintains tissue homeostasis. So far, more than 20 different Cxs in mammals have been reported. Each of them shows specific tissue distribution, electrophysiological characteristics, and regulatory properties [106]. In human skin and appendages, at least nine Cx members are expressed and show spatial and differential expression patterns. For example, Cx43 is most abundantly expressed throughout spinous and granular layers but focally in the basal layer in interfollicular epidermis [112]. Cx26 is weakly expressed in the basal layer of interfollicular epidermis but prominently expressed in palmoplant ar epidermis [112]. Both Cx43 and Cx26 are strongly expressed in the hair follicle ORS and IRS [112]. In addition, the expression of Cx30 is detected in the upper layer of the palmoplantar epidermis as well as the hair follicle ORS, but not in the interfollicular epidermis [26]. The expression pattern of these Cxs changes dramatically in abnormal situations such as wound healing, hyperproliferative disorders, and skin tumors. For instance, in psoriatic plaques, Cx26 is detected throughout all layers of the epidermis [61], and Cx30 is expressed even in interfollicular epidermis [69]. By contrast, significant reduction of GJs and loss of Cx expression have been reported in epidermal neoplasia [52, 153]. These data suggest that GJs are largely involved in cell proliferation, differentiation, and intercellular signaling in the skin.

6.10.2 Experimental Techniques

To date, knockout mice for several Cxs that are expressed in the hair follicle have been reported [105, 138]; however, these mice do not show evidence of hair symptoms. Instead, in vitro studies based on mutations in human Cxs have been performed.

6.10.3 Clinical Relevance

Clouston syndrome or hidrotic ectodermal dysplasia (OMIM 129500) is an autosomal dominant disease characterized by palmoplantar hyperkeratosis, partial to complete alopecia, and nail defects. In 2000, the disease was shown to be caused by missense mutations in the Cx30 gene (*GJB6*) [62]. The functional consequences of two of these mutations, G11R and A88V, have been analyzed in vitro [17]. Common et al. [17] transfected vectors expressing either G11R-Cx30 or A88V-Cx30 to cultured cells, which demonstrated that both mutations impaired trafficking of the protein to the plasma membrane. However, Essenfelder et al. [25] later showed that when these mutant proteins were co-expressed with wild-type Cx30 protein, the trafficking of mutated Cx30 proteins to the plasma membrane was detected at the site where both mutated and wild-type Cx30 proteins co-localized [25]. Furthermore, the mutated Cx30 proteins formed abnormal but functional hemichannels that caused a leakage of adenosine triphosphate (ATP) into the extracellular medium, indicating that the mechanism for the disease is a gain of function rather than a loss of function [25].

The keratitis-ichthyosis-deafness syndrome (KID; OMIM 148210) is an autosomal-dominant disease characterized by vascularizing keratitis, profound sensorineural hearing loss, and severe erythrokeratoderma. Patients with KID syndrome also show congenital atrichia or scarring alopecia in high frequency. Heterozygous missense mutations in the Cx26 gene (GJB2) have been shown to cause KID syndrome [107]. Furthermore, it has been reported that a heterozygous mutation (V37E) in the *GJB6* gene resulted in a phenotype similar to KID disease [49]. This mutation was previously detected in another family with Clouston syndrome [129]. Likewise, a N14K mutation in the *GJB2* gene has been identified in a patient showing a Clouston-syndrome-like phenotype [142]. These data indicate the genetic heterogeneity of Clouston and KID syndromes. So far, all the pathogenic mutations for both diseases have been identified in cytoplasmic N-terminus transmembrane domains 1 and 2, and extracellular domain 1 of either Cx26 or Cx30 (Fig. 6.11), which suggests the functional importance of these domains. In addition to Cx26 and Cx30, Kjaer et al. [55] have recently reported that a heterozygous mutation in the Cx43 gene (*GJA1*) is associated with curly hair phenotype in a family with oculo-dento-digital dysplasia (OMIM 164200) [55].

6.11 Lipase H

6.11.1 Structure and Function/ Pathophysiology/Developments

Lysophosphatidic acid (LPA) is an extracellular lipid mediator that has multiple biological functions, such as cell proliferation, anti-apoptotic activity, and cytoskeletal organization. LPA functions through G-protein-coupled receptors, which consequently activate intracellular signaling pathways [85]. Phospholipase A1 (PLA1) and PLA2 are involved in the production of LPA, through the hydrolysis of phosphatidic acids [23, 29, 121]. To date, several types of PLA have been identified in humans. In 2002, two groups cloned the *LIPH* gene encoding a new member of PLA1, named lipase H (alternatively known as membrane-associated phosphatidic acid-selective phospholipase A1 alpha), on human chromosome 3q27-q28 [50, 130]. Lipase H shows high homology with other PLA1 members, lipase I and phosphatidylserine-specific phospholipase A1. The recombinant lipase H protein is exclusively localized to the plasma membrane and has the ability to produce LPA [130]. In addition, the *LIPH* mRNA has been shown to be expressed abundantly in prostate, testis, ovary, colon, pancreas, kidney, and lung [50, 130]. However, its expression and relevance in the skin and hair follicle were only recently elucidated.

6.11.2 Experimental Techniques

Most recently, linkage and positional cloning studies in families with a rare form of congenital hypotrichosis have revealed a relationship between lipase H and the hair follicle (see Sect. 6.11.3).

6.11.3 Clinical Relevance

Kazantseva et al. [53] screened about 350,000 individuals in two populations from the Volga-Ural region of Russia. These populations have many families with an autosomal recessive form of hair loss and hair growth defects (hypotrichosis, total, Mari type; OMIM 604379). Affected individuals are characterized by deficiencies of hair growth on the scalp and body starting at birth, without any other abnormalities. The growth of scalp hairs is retarded or arrested, leading to short hair shaft length. Hair shafts of affected individuals often show trichorrhexis nodosa, which reflects fragility of the hairs. In addition, histopathological analysis demonstrated keratotic plugs within a dilated infundibulum,

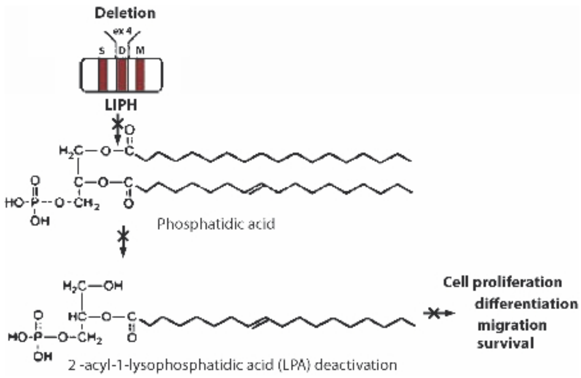


Fig. 6.12 Schematic representation of the role of lipase H as well as a mechanism to cause the disease by *LIPH* mutation. Lipase H protein possesses three catalytic residues: S154, D178, and H248. The deleted protein lacks D178, which is predicted to result in the loss of ability to produce lysophosphatidic acid (*LPA*) from phosphatidic acid. With permission of Kazantseva et al. [53]

indicating abnormal keratinization. Linkage analysis resulted in the identification of a homozygous mutation in the *LIPH* gene of all affected individuals analyzed [53]. The founder mutation is a 985-bp deletion including exon 4 of the *LIPH* caused by short interspersed nuclear element-retrotransposon-mediated recombination, which is predicted to generate truncated lipase H protein lacking 34 amino acids. As the deleted region is highly conserved among different species and contains a putative catalytic amino acid residue (N178), the aberrant lipase H is most likely to lose its enzymatic activity. Recent studies have shown that knockout mice for lipase I, which has a high homology and similar expression pattern to lipase H, die by the age of 10–15 days due to a severe defect in triglyceride metabolism [145, 146]. In addition, a mutation in lipase I causes hypertriglyceridemia in humans [146]. Therefore, it is somewhat surprising that mutated lipase H results in only a hair phenotype in humans. Reverse transcription-polymerase chain reaction (RT-PCR) experiments have demonstrated that the LIPH transcripts are strongly expressed in the hair follicle and the expression levels are much higher than those of other known lipase members [53]. These data indicate that dysfunction of lipase H can be compensated in internal organs, but not in the hair follicle. Even though the detailed expression pattern and biological function of lipase H in the hair follicle remain largely unknown, the loss-of-function mutation in *LIPH* diminishes the production of LPA mediators, leading to an effect on the migration, differentiation, or proliferation of cells in the hair follicle (Fig. 6.12).

Table 6.1 Causative genes for syndromic and non-syndromic hair diseases. (*AD* Autosomal dominant, *AR* autosomal recessive, *XR* X-linked recessive)

Disease name		OMIM	Inheritance pattern	location	Gene symbol
Syndromic hair diseases	Hypohidrotic ectodermal dysplasia	305100 129490/224900 224900	XR AD/AR AR	Xq12-13 2q11-13 1q42.2-43	EDA EDAR EDARADD
	Hypotrichosis with juvenile macular dystrophy	601553	AR	16q22.1	CDH3
	Ectodermal dysplasia, ectrodactyly, macular dystrophy (EEM syndrome)	225280	AR	16q22.1	CDH3
	Vitamin D-dependent rickets type IIA	277440	AR	12q13.11	VDR
	T-cell immunodeficiency, congenital alopecia, and nail dystrophy (human nude phenotype)	601705	AR	17q11-12	FOXN1
	Ectodermal dysplasia/skin fragility syndrome	604536	AR	1q32	PKP1
	Naxos disease	601214	AR	17q21 6p24	JUP DSP
	Skin fragility-woolly hair syndrome	607655	AR	6q24	DSP
	Hidrotic ectodermal dysplasia (Clouston syndrome)	129500	AD	13q11-q12	GJB6, GJB2
	Keratitis-ichthyosis-deafness syndrome	148210	AD	13q11-q12	GJB2, GJB6
Non-syndromic hair diseases	Atrichia with papular lesions	209500	AR	8q21.2	HR
	Monilethrix	158000	AD	12q13	KRTHB1 (KRT81) KRTHB3 (KRT83)
	Localized autosomal recessive hypotrichosis/monilethrix	607903	AR	18q21.1	KRTHB6 (KRT86) DSG4
	Hypotrichosis simplex of the scalp	146520	AD	6q21.3	CDSN
	Hypotrichosis, total, Mari type	604379	AR	3q27	LIPH
	Autosomal recessive woolly hair/hypoerichosis simplex	278150/146520	AR	13914	P2RY5

6.12 P2RY5

Although several human syndromes are known to show woolly hair as a part of the phenotype, such as Naxos disease [73], simple autosomal recessive inheritance of isolated woolly hair has only rarely been reported [45, 111]. We recently identified pathogenic mutations in the P2RY5 gene in consanguineous Pakistani families with autosomal recessive woolly hair (OMIM 278150) [124]. The P2RY5 gene resides on human chromosome 13q14 and encodes a G protein-coupled receptor (GPCR) [41]. We showed that P2RY5 protein is abundantly expressed in both Henle's and Huxley's layers of the hair follicle inner root sheath, which is an important component for shaping the growing hair [124]. Interestingly, mutations in the P2RY5 gene in Saudi Arabian families with autosomal recessive hypotrichosis simplex (OMIM 146520) have also been demonstrated, as well as evidence that P2RY5 is a receptor of LPA [100]. As described in sect. 6.11, Lipase H generates LPA from phosphatidic acids [130], and disruption of Lipase H causes an autosomal recessive hypotrichosis [53]. Taken together, these findings provide a new insight into a crucial role of Lipase H/LPA/GPCR signaling in hair follicle development and hair growth, which can influence both hair texture and density.

6.13 Outlook – Future Developments

Screening of different populations of hair follicle cells with microarray techniques [94, 141] and the production of new mouse mutants will enable us to understand the function of genes that are involved in hair follicle morphogenesis and/or cycling. In addition, further linkage analysis of families with hair symptoms will lead to the identification of novel disease genes. For example, Djabali et al. [22] previously performed linkage analysis on two Arab families with Naxos disease and excluded gene loci for all known desmosomal components including *JUP* and *DSP,* which suggests that the disease shows further genetic heterogeneity. We anticipate that identification of causative genes for hair diseases and improved understanding of the function of these genes will enable us to establish effective therapies in the future. It is well known that the hair follicle bulge possesses self-renewal and multipotent stem cells [12, 86, 95, 137]. Cultured keratinocytes derived from single bulge cells, when grafted onto back skins of nude mice with dermal fibroblasts, have been shown to form mature hair follicles [12]. Thus, gene transfer to hair follicle bulge cells may become an ideal target for gene therapy. In addition, recently developed gene-silencing techniques such as small interference RNA and RNA-DNA oligonucleotide will be useful therapeutic approaches for hair diseases, especially those caused by dominant mutations.

Summary for the Clinician

Hair diseases can be classified into two large groups: syndromic (hair phenotype as part of a syndrome) and non-syndromic (hair phenotype only) hair diseases (Table 6.1). Most hair diseases are syndromic, therefore the clinician should always keep in mind that the hair phenotype might be a sign of an underlying disease such as cardiomyopathy in Naxos disease. Our knowledge of the genetic background to hair diseases, which is described in this chapter, will allow early diagnosis and potential therapeutic intervention for many congenital diseases with a hair phenotype.

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Chapter 7

Histology of the Human Hair Follicle

David A. Whiting

7

Synonyms

follicular dermal sheath: follicular fibrous sheath, follicular stela: follicular angiofibrotic streamer, hair fiber: hair shaft, hair bulb: hair root, horizontal section: transverse section, hyaline membrane: vitreous or glassy membrane, outer root sheath: trichilemma, vellus-like hair: miniaturized hair

Key Features

- Recognition of the microscopic appearances of normal cycling human hair follicles is important for clinicians and researchers.
- First step is to take a full-thickness, 4-mm punch biopsy of the scalp.
- For three-dimensional evaluation, vertical and horizontal sections may be needed.
- Follicular changes in anagen, catagen, and telogen need to be recognized.
- Follicular counts in horizontal sections are valuable in the diagnosis and treatment of hair disorders, especially the non-cicatricial alopecias.

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7.1 Introduction

Vertical sections of scalp biopsy samples have provided the traditional view of hair follicles; indeed, most anatomical and histopathological features of hair follicles have been described in vertical sections. However, recently, the value of horizontal (transverse) sectioning has been recognized. In fact, a thorough knowledge of follicular anatomy in both planes is needed to obtain maximum information from scalp biopsy samples.

7.2 History

Considerable knowledge of hair follicle anatomy was amassed by histologists in Europe in the nineteenth and early twentieth centuries. Further progress was made later in the twentieth century in research and symposia directed by William Montagna. The concept of horizontal sectioning was introduced by Headington in 1984 and an increasing number of dermatopathologists now interpret horizontal sections.

7.3 Structure and Function

Hair follicles comprise a permanent upper segment of follicular infundibulum and isthmus, and an impermanent lower segment of lower follicle and bulb. They cycle continuously through periods of growth and rest, namely anagen and telogen. The lower segment is responsible for generation of the growing hair and disappears during the resting phase. The cylindrical hair fiber is extruded continuously during the growth phase. The hair fiber cortex consists of keratin filaments embedded in a sulfur-rich matrix, enclosing the medulla and surrounded by the cuticle of the hair shaft. It is generated by transient amplifying matrix cells in the hair bulb, which surround the dermal papilla. The hair fiber diameter remains uniform during a single growth phase under normal conditions. The entire hair follicle is enclosed by the outer root sheath or trichilemma, which extends from the hair bulb to the skin surface epidermis lining the infundibulum. The inner root sheath invests the growing hair fiber from bulb to mid-isthmus level [6, 8, 12].

Human hairs grow to a specific length, which varies with the individual. Hair length depends on genetic influences, body site, climate, age, and nutritional, hormonal and other factors. Hair length is determined by the rate and duration of anagen. Scalp hair grows an average of 1 cm per month and the anagen growth phase lasts 1–7 years; therefore, scalp hairs can grow 12–84 cm in length. Hairs of different diameters are commonly found in the same scalp [12].

Cortical fibers are responsible for the mechanical properties of hair and are bound together by hair shaft cuticle cells. Hair shaft and inner root sheath cuticles interlock to stabilize the growing hair and ensure that the inner root sheath and hair shaft grow upward together.

On a normal scalp there are 100,000–150,000 scalp hairs, of which 90%–95% are growing and 5%–10% are resting. The telogen or resting phase lasts 3 months (range 2–4 months). Adjacent hairs cycle independently so that shedding is scattered and inconspicuous rather than localized and obvious. Hair is subject to weathering from normal wear and tear, and keratinized hair cannot repair itself. However, hair will replace itself, with new hair growing in after the old hair is shed. Therefore, hair cycling is of paramount importance.

Hair development starts after 8 weeks of fetal life with the appearance of placodes in the epidermal basal layer, above underlying dermal condensates of mesothelial cells [1, 5]. Epidermal pegs grow down to enclose these dermal papillary cells. When downward extension and follicular formation are complete, hair growth ensues and the initial hair population is complete by 22 weeks.

Fine lanugo hair develops in an advancing wave from the frontal to the occipital scalp and is shed by 36 weeks' gestation. A second coat of lanugo hair appears and it is shed in a synchronized wave pattern at 3–4 months of life. The bare occipital patch often seen in infants is usually physiological, resulting from synchronized shedding of the final wave of lanugo telogen hairs prior to their replacement by normal scalp hairs [7]. The maximum number of scalp hair follicles during the human life span is present at birth; thus, hair follicle density is greatest in neonates and lessens progressively during childhood and adolescence as the scalp stretches over the growing skull until it stabilizes in adults (250–350 hairs per cm^2) [12].

7.4 Normal Hair Growth Cycle

Synchronized follicular cycling is lost after 1 year of life and is replaced by a random or mosaic pattern of asynchronous hair cycling. Established scalp hair follicles cycle continuously during their life span through stages of growth, rest, shedding, and regrowth [4, 9, 10]. Scalp hairs comprise large terminal hairs and small vellus hairs. The average ratio of terminal to vellus hairs in a normal scalp equals 7:1.

Terminal hairs are conspicuous and exceed 0.03 mm in diameter and 1 cm in length, and may be pigmented

and medullated. Terminal hairs can be graded by hair shaft diameter as small (0.031–0.06 mm), medium (0.061–0.09 mm), or large (greater than 0.091 mm). Vellus hairs are inconspicuous and are 0.03 mm or less in diameter and often less than 1 cm in length and lack melanin and medulla [3]. Terminal hairs miniaturized to vellus hair proportions are described as vellus-like hairs. Terminal hairs are rooted in subcutaneous tissue or deep dermis, whereas vellus hairs are rooted in the upper dermis.

Termination of the growing or anagen phase is marked by the intermediate or catagen phase, which lasts approximately 2 weeks. In catagen, the hair shaft retreats upwards and the outer root sheath shrinks by individual cell death, also known as apoptosis. In catagen, the lower follicle disappears leaving an angiofibrotic strand or streamer (stela) indicating the former position of the anagen root.

The ensuing telogen phase lasts an average of 3 months before a new anagen hair develops. In telogen, the resting club root is situated at the "bulge" level, where the arrector pili muscle inserts into the hair follicle [2]. The telogen bulb lacks pigment and an inner root sheath. The hair shaft is surrounded by trichilemmal keratin and the trichilemma (outer root sheath). The telogen hair is shed during the exogen phase, which occurs in either late telogen or early anagen. Assuming there are 100,000 scalp hairs with 10% in telogen, the average hair loss equals 100 per day.

The next anagen cycle begins with enlargement of the dermal papilla at the "bulge" level and the formation of a new anagen bulb [2], which starts growing down the follicular stela towards its point of origin in the subcutaneous tissue.

7.5 Biopsies of Human Scalp

To standardize data, a disposable 4-mm biopsy punch is recommended. Local anesthesia with lidocaine and epinephrine is suggested, subject to patient hypersensitivity. Start the biopsy punch in the same direction as the hairs and extend the biopsy deep into subcutaneous tissue. Two biopsy samples are needed for adequate vertical and horizontal sectioning [12].

7.5.1 Vertical Section

Rotate the biopsy specimen until the hairs are pointing straight upwards at 90° and bisect the specimen in that plane. Mount both halves in the block with the cut surface downward, or keep one-half for fresh tissue stains or other purposes. Take three successive sections initially and more if needed [12].

7.5.2 Horizontal Section

Bisect biopsy specimen horizontally exactly parallel to the epidermis, 0.5–1 mm below the dermoepidermal junction. Mount both portions together in the block with the cut surfaces downward. Take 12 successive sections initially and more if needed until the correct planes through both papillary and reticular dermis are seen [12].

7.6 Follicular Anatomy

7.6.1 Terminal Anagen Hair

The terminal anagen hair extends from its bulb in the subcutaneous tissue to its point of emergence in the upper dermis through the follicular infundibulum. The impermanent lower segment comprises the lower follicle and hair root. The permanent upper follicle segment comprises the infundibulum and isthmus (Figs. 7.1, 7.2, 7.3).

7.6.2 Hair Bulb

The follicular root consists of the hair bulb, which surrounds the dermal papilla containing connective tissue cells and blood vessels (Figs. 7.4, 7.5). The papilla is surrounded by undifferentiated, actively dividing hair matrix cells in the lower bulb. Melanocytes are usually present at the apex of the dermal papilla and hair matrix cells in this vicinity give rise to hair medullary cells. Hair matrix cells around this central area produce elongated cortical cells, which stream upward to form the developing hair shaft. Higher up in the keratogenous zone, these cells become compacted into hard keratin. The outer fringe of matrix cells forms the hair cuticle and the surrounding inner root sheath. The hair cuticle invests the hair fiber with six to ten overlapping layers of cuticle cells. Cuticle cells keratinize and project outwards and forwards to interlock with the inwardly projecting cuticle cells of the inner root sheath [12].

The inner root sheath surrounds the hair fiber and comprises three layers: the innermost layer forms the cuticle of the inner root sheath comprising overlapping elongated cells, which slant downward; the middle layer of Huxley comprises three to four layers of cuboidal cells; and the outer layer of Henle comprises a single

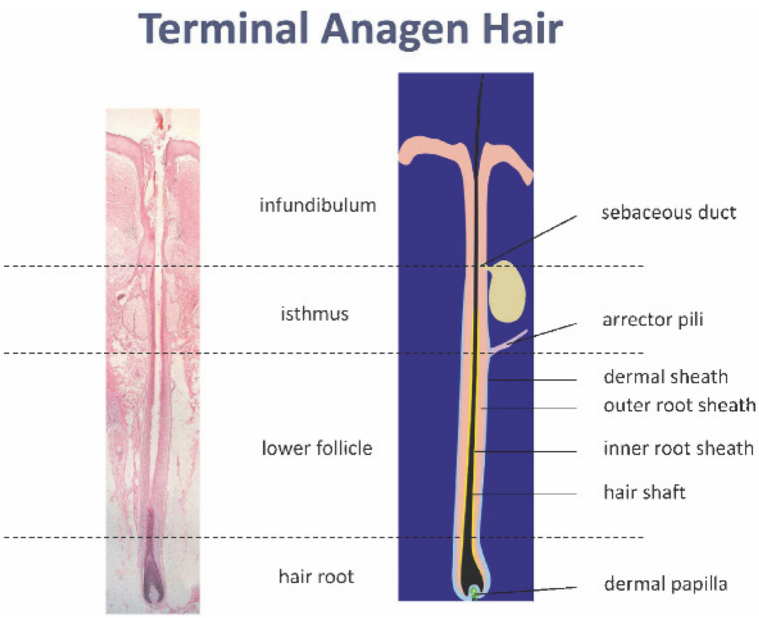


Fig. 7.1 Terminal anagen hair: the follicular segments comprise infundibulum, isthmus, lower follicle and hair root, demarcated by the sebaceous duct, arrector pili insertion and top of the hair bulb. Reprinted from [12] with permission from Canfield Publishing

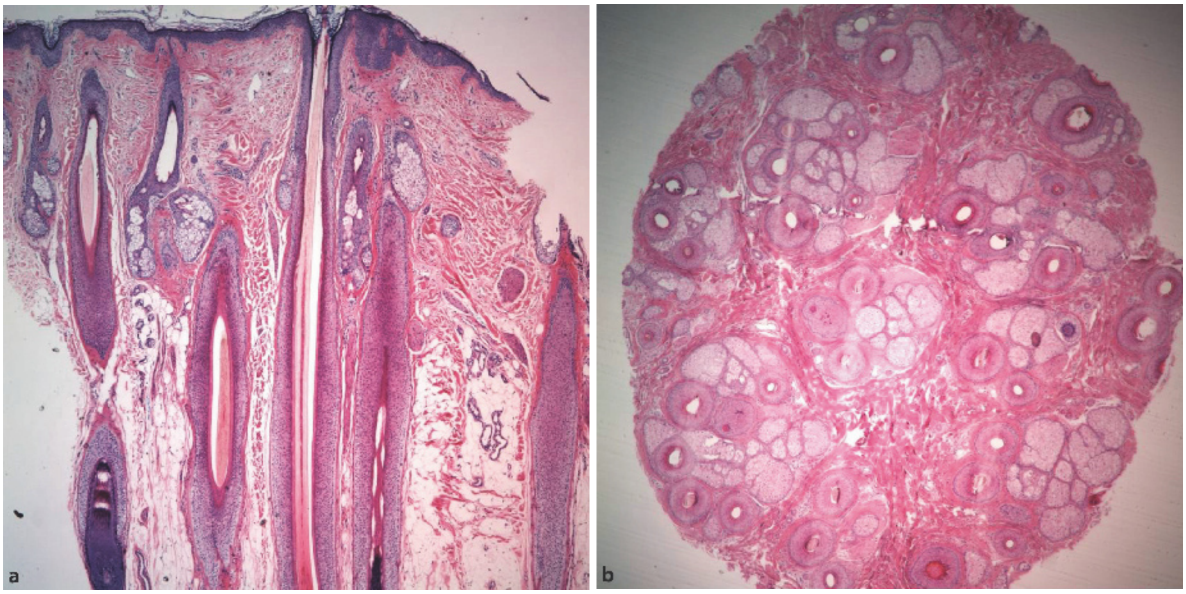


Fig. 7.2 **a** Vertical section: upper and mid dermis – terminal and vellus follicles. (hematoxylin and eosin stain, original magnification 40×). **b** Horizontal section: upper dermis – sebaceous gland level – terminal and vellus follicles (hematoxylin and eosin stain, original magnification 40×)

layer of elongated cells. The inner root sheath is surrounded by one or more layers of cells of the outer root sheath or trichilemma [12].

The potential space between inner and outer root sheaths is named the companion layer and it allows the inner root sheath to slide upward over the outer root sheath during hair growth. The outer root sheath, or trichilemma, is covered by the hyaline or vitreous membrane, which is continuous with epidermal basement membrane surrounding the dermal papilla. Folds or corrugations of the hyaline membrane are sometimes seen projecting into the underlying trichilemmal layer.

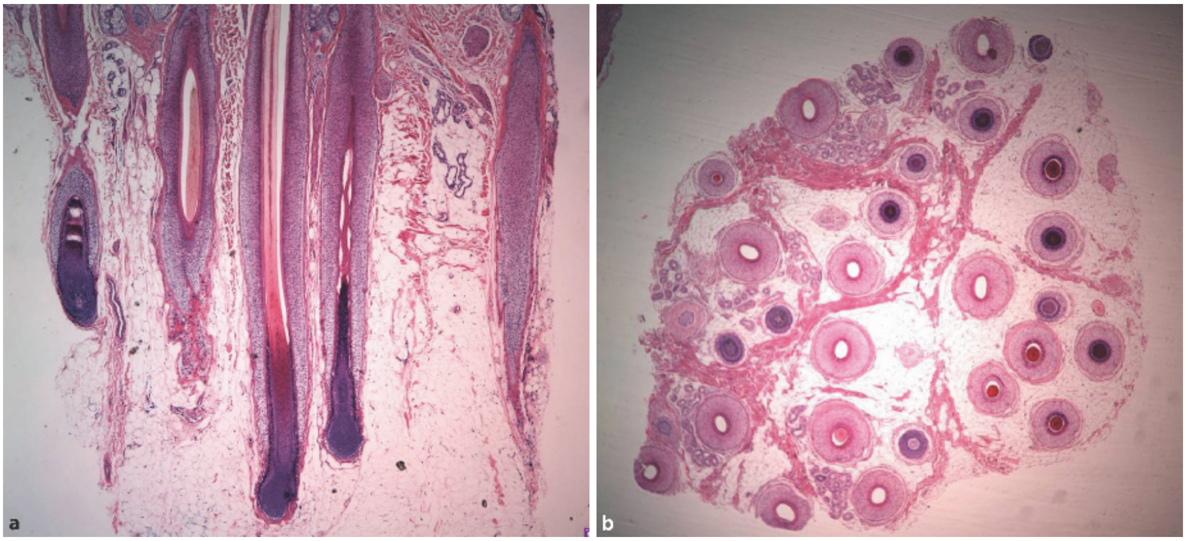


Fig. 7.3 **a** Vertical section: lower and mid dermis – terminal follicles and bulbs (hematoxylin and eosin stain, original magnification 40×). **b** Horizontal section: lower dermis and subcutaneous fat – terminal follicles and bulbs (hematoxylin and eosin stain, original magnification 40×)

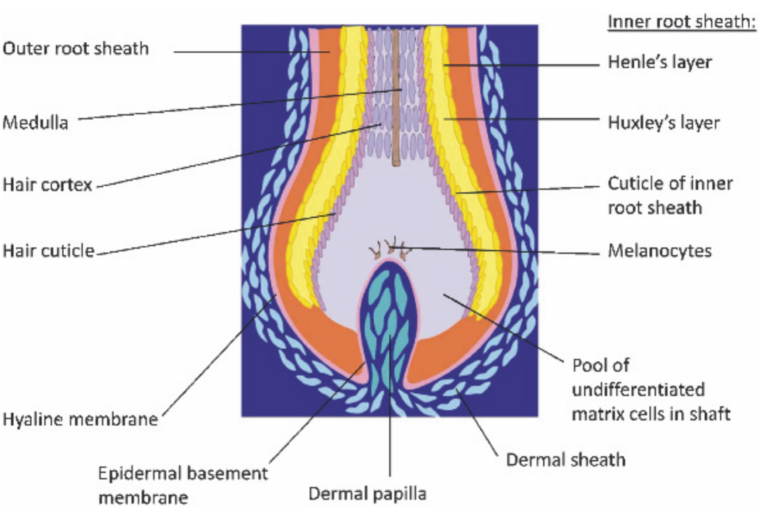


Fig. 7.4 The hair bulb is surrounded by the dermal sheath, which is continuous with the dermal papilla, and the hyaline membrane beneath it, which joins the epidermal basement membrane around the dermal papilla. Next is the outer root sheath followed by the inner root sheath comprising Henle's layer, Huxley's layer and the cuticle of the inner root sheath. The central developing hair shaft is largely comprised of hair cortex invested by its cuticle and surrounding the medulla. Reprinted from [12] with permission from Canfield Publishing

The hyaline membrane is surrounded by the fibrous dermal sheath of the hair follicle, which is continuous with the dermal papilla at the base of the hair bulb.

Proceeding from the hair bulb up to the lower follicle, the inner and outer root sheaths thicken and become well demarcated. Henle's layer keratinizes first, with the appearance of trichohyaline granules near the hair bulb, forming a distinct pinkish keratinized band higher up from the bulb (Fig. 7.6a,b).

The cuticle of the inner root sheath is the next to keratinize, synchronizing with keratinization of the cuticle of the hair shaft (Fig. 7.7).

Finally, trichohyaline granules appear in Huxley's layer, signaling impending keratinization (Fig. 7.8).

Keratinization of the inner root sheath is completed half way up the lower follicle, such that the keratinized inner root sheath occupies the upper half of the lower follicle (Fig. 7.9).

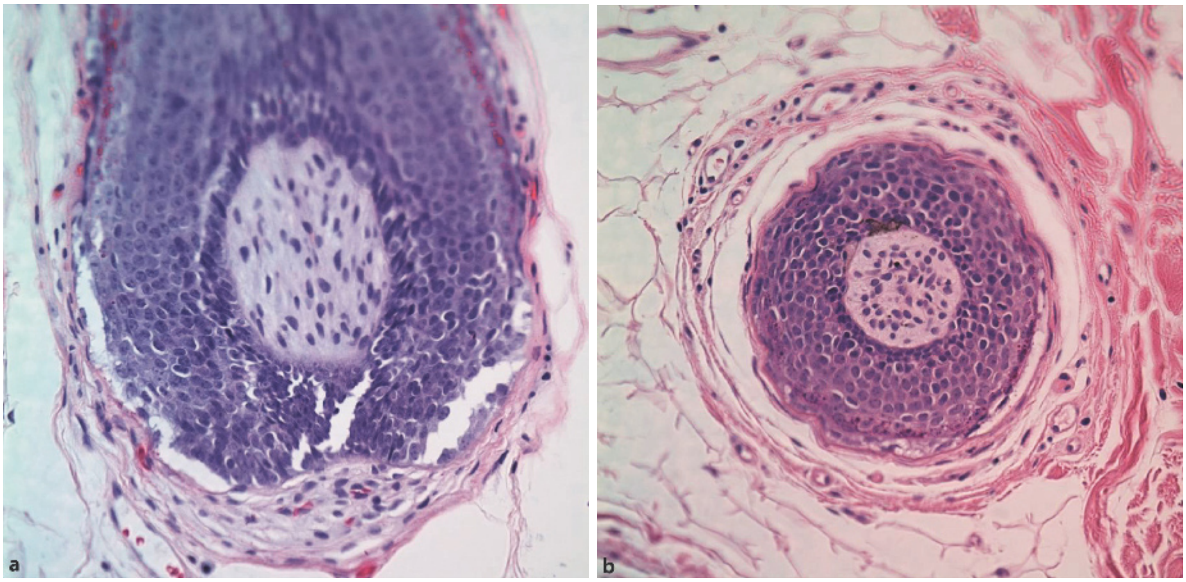


Fig. 7.5 **a** Lower bulb, vertical section: dermal papilla enclosed by hair matrix cells, surrounded by dermal sheath (hematoxylin and eosin stain, original magnification 40×). **b** Lower bulb, horizontal section: dermal papilla with papillary cells and connective tissue invested by hair matrix cells surrounded by the dermal sheath (hematoxylin and eosin stain, original magnification 40×)

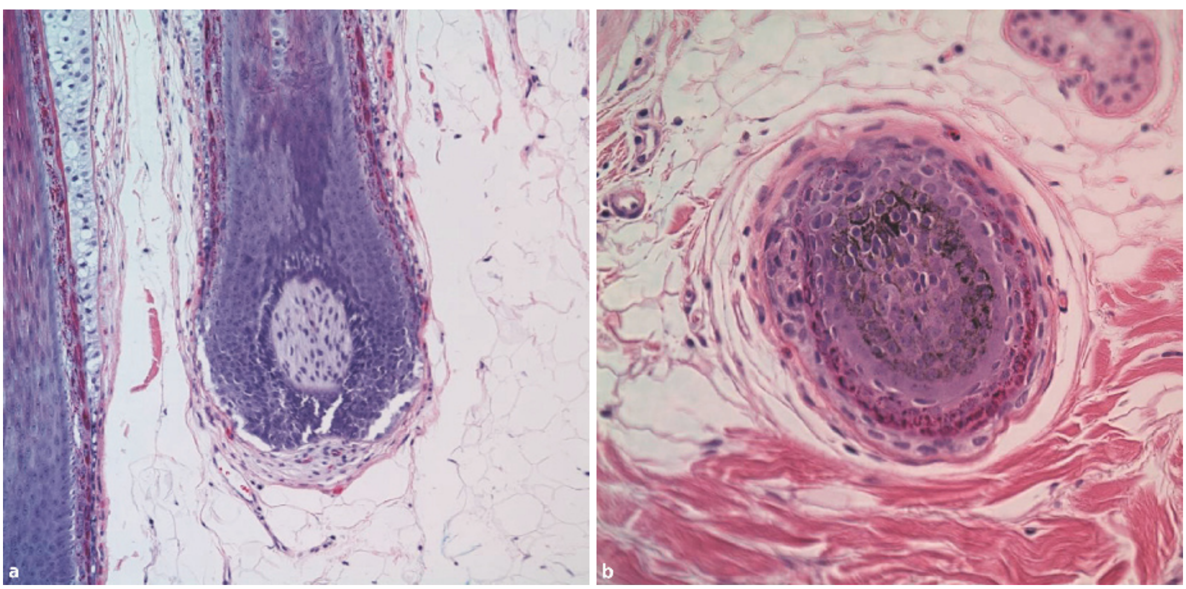


Fig. 7.6 **a** Upper bulb, vertical section: the developing proximal hair shaft shows an emerging central medullary cavity, surrounded by developing cortex, invested by inner and outer root sheaths and the dermal sheath. Henle's layer, the outermost of the three layers of the inner root sheath, is beginning to keratinize (hematoxylin and eosin stain, original magnification 200×). **b** Upper bulb, horizontal section: the central developing hair fiber is surrounded by inner and outer root sheaths and dermal sheath, with commencing keratinization of Henle's layer, the outermost layer of the inner root sheath (hematoxylin and eosin stain, original magnification 200×)

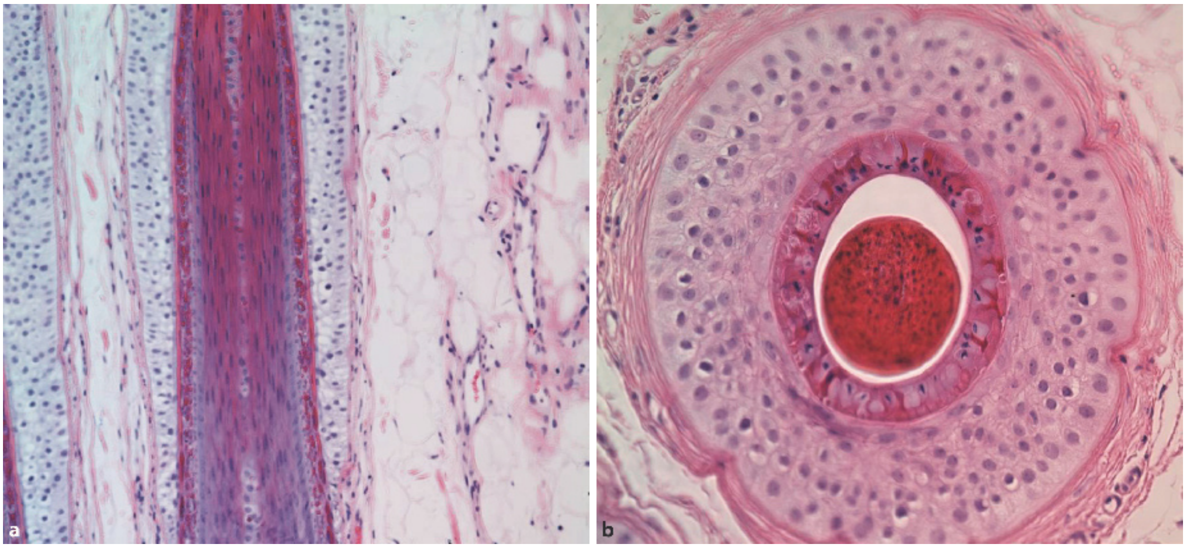


Fig. 7.7 **a** Suprabulbar lower follicle, vertical section: keratinization occurs in the cuticle of the inner root sheath and in the cuticle of the hair shaft (hematoxylin and eosin stain, original magnification 200×). **b** Suprabulbar lower follicle, horizontal section: the cuticle of the central hair shaft and the cuticle of the inner root sheath are both keratinized (hematoxylin and eosin stain, original magnification 400×)

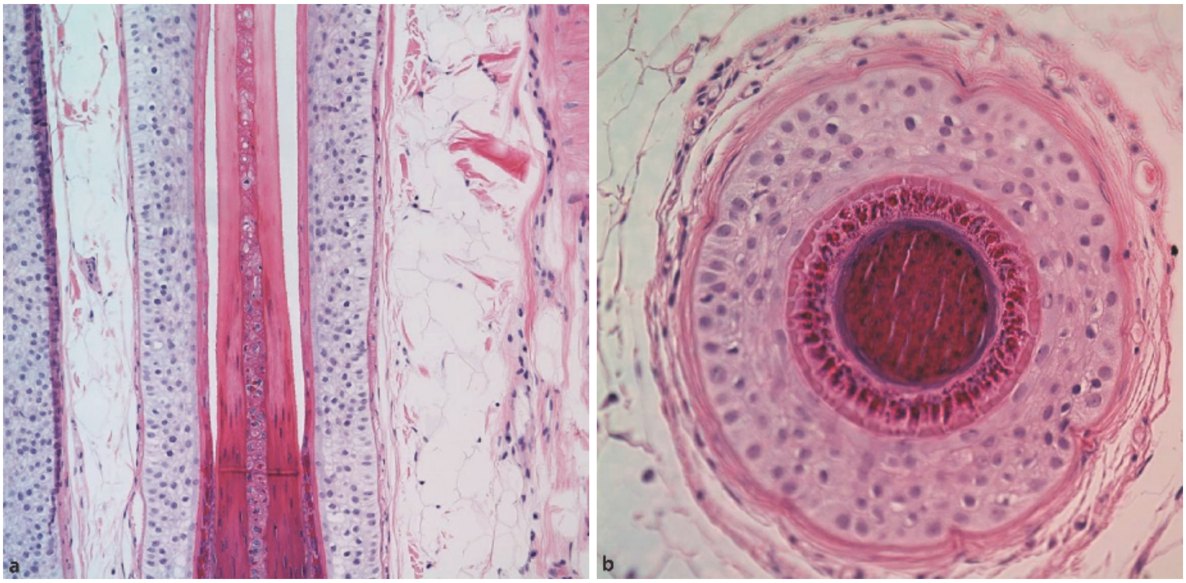


Fig. 7.8 **a** Intermediate lower follicle, vertical section: keratinization of Huxley's layer is seen in the lower portion of this section, leading to a fully keratinized inner root sheath higher up (hematoxylin and eosin stain, original magnification 200×). **b** Intermediate lower follicle, horizontal section: impending keratinization of Huxley's layer in central layer of inner root sheath is signaled by the red stained keratohyaline granules (hematoxylin and eosin stain, original magnification 400×)

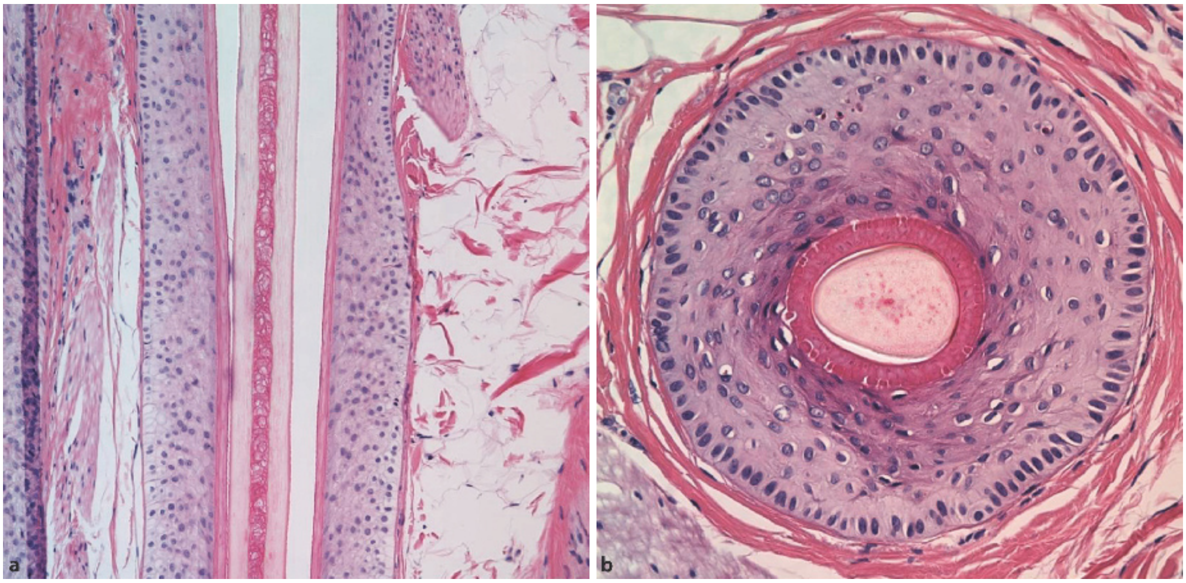


Fig. 7.9 **a** Upper half, lower follicle, vertical section: hair shaft and inner and outer root sheaths are fully keratinized (hematoxylin and eosin stain, original magnification 200×). **b** Upper half, lower follicle, horizontal section: hair shaft and inner and outer (trichilemmal) sheaths are fully keratinized (hematoxylin and eosin stain, original magnification 400×)

7.6.3 Isthmus

The isthmus extends upwards from the arrector pili muscle insertion (bulge area) to the entry of the sebaceous duct. The inner root sheath crumbles and disappears in the mid-isthmus of the upper follicle (Fig. 7.10). There it is replaced by trichilemmal keratin formed by the outer root sheath or trichilemma. Trichilemmal keratin lines the upper isthmus extending to the level of entry of the sebaceous duct at the base of the infundibulum (Fig. 7.11) [12].

The infundibulum is lined by epidermis with a granular layer and basket weave keratin, which is continuous with the skin surface epidermis (Fig. 7.12). The hair shaft has no secure attachment to isthmus or infundibulum, which allows freedom of movement.

7.6.4 Follicular Units

Horizontal sections at the sebaceous duct level show follicular units. Follicular units are roughly hexagonal in shape and are surrounded by a loose network of collagen; they contain several terminal and vellus follicles with sebaceous ducts and glands and arrector pili muscles (Fig. 7.13) [3]. In adults, the mean area of a follicular unit is 1 mm^2; thus 12–14 follicular units are usually found in a horizontal section of a 4-mm punch biopsy, which has an actual area of 12.57 mm^2.

7.6.5 Vellus Hairs

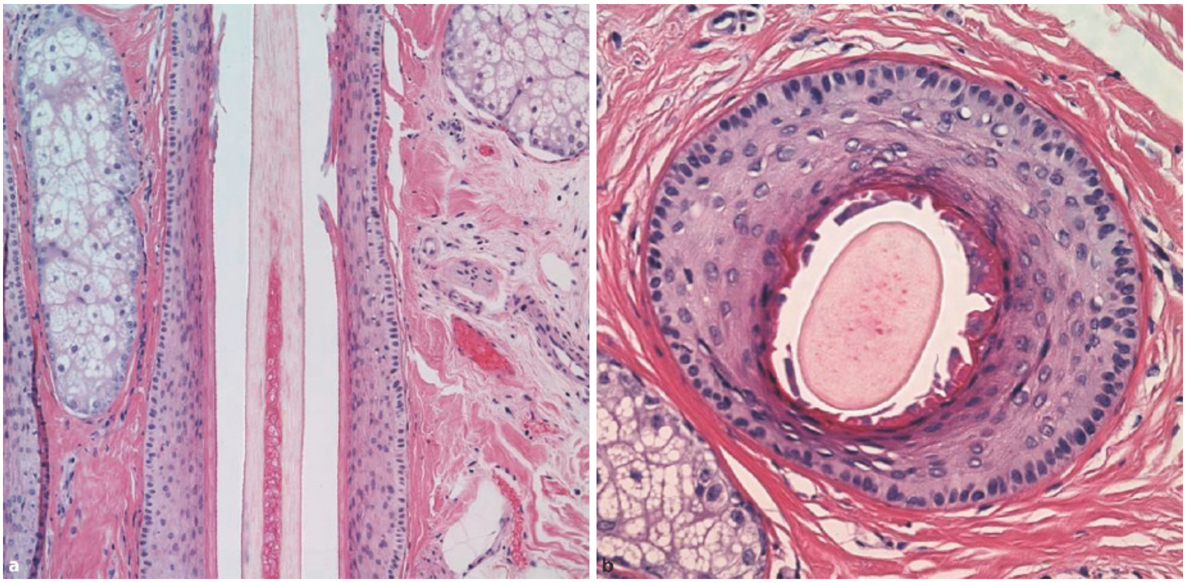
Vellus hairs are rooted in papillary or upper reticular dermis. Vellus hairs do not contain a medullary cavity or melanin. The vellus hair diameter is 0.03 mm or less and is often less than the thickness of its inner root sheath [3]. True vellus hairs have thin external root sheaths and short stelae in the upper dermis. Vellus-like miniaturized hairs have thicker external root sheaths and long stelae extending into lower dermis or subcutaneous fat [12]. Hairs are typically miniaturized by androgenetic alopecia or by alopecia areata. Follicular stelae, in upper dermis only, indicate vellus hairs. Follicular stelae in lower dermis indicate terminal, catagen or telogen hairs or miniaturized vellus-like hairs (Figs. 7.14, 7.15).

7.6.6 Catagen and Telogen Phase

7.6.6.1 Terminal Catagen Hair

When anagen ends, hair goes into catagen, the intermediate, transition stage between growth and rest, for 10–14 days. Because catagen hairs inevitably become telogen hairs, catagen is included in the telogen phase when calculating anagen and telogen percentages.

As catagen begins, the hair shaft and bulb start retracting upward leaving behind an angiofibrotic streamer or stela linking the follicle to the site of the former anagen



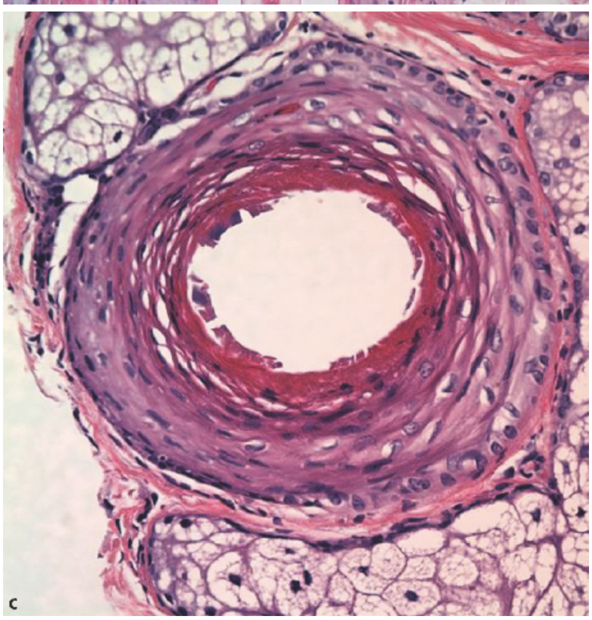


Fig. 7.10 **a** Mid-isthmus, vertical section: grayish inner root sheath is crumbling and disappearing (hematoxylin and eosin stain, original magnification 200×). **b** Mid-isthmus, horizontal section: gray staining inner root sheath is crumbling and being replaced by red staining trichilemmal keratin from outer root sheath (trichilemma) (hematoxylin and eosin stain, original magnification 400×). **c** Mid-isthmus, horizontal section: vanishing inner root sheath (hematoxylin and eosin stain, original magnification 400×)

bulb. The hair shaft and inner root sheath slide upward together inside the outer root sheath leaving an elongated mass of trichilemmal outer root sheath below. Apoptosis of trichilemmal cells produces a marked shrinkage of the outer root sheath, accompanied by thickening and wrinkling of the surrounding hyaline layer (Figs. 7.16, 7.17).

As the hair shaft retreats further upwards, its base becomes club-shaped and is surrounded by a pocket of trichilemmal keratin. The vestigial bulb and dermal papilla trail beneath linked to the follicular stela [3].

In horizontal sections, the catagen hair is generally round or oval and is surrounded by a thickened hyaline membrane, often convoluted due to a concertina-like compression effect from the ascending hair bulb. The catagen hair usually contains apoptotic cells, which stain reddish with hematoxylin and eosin.

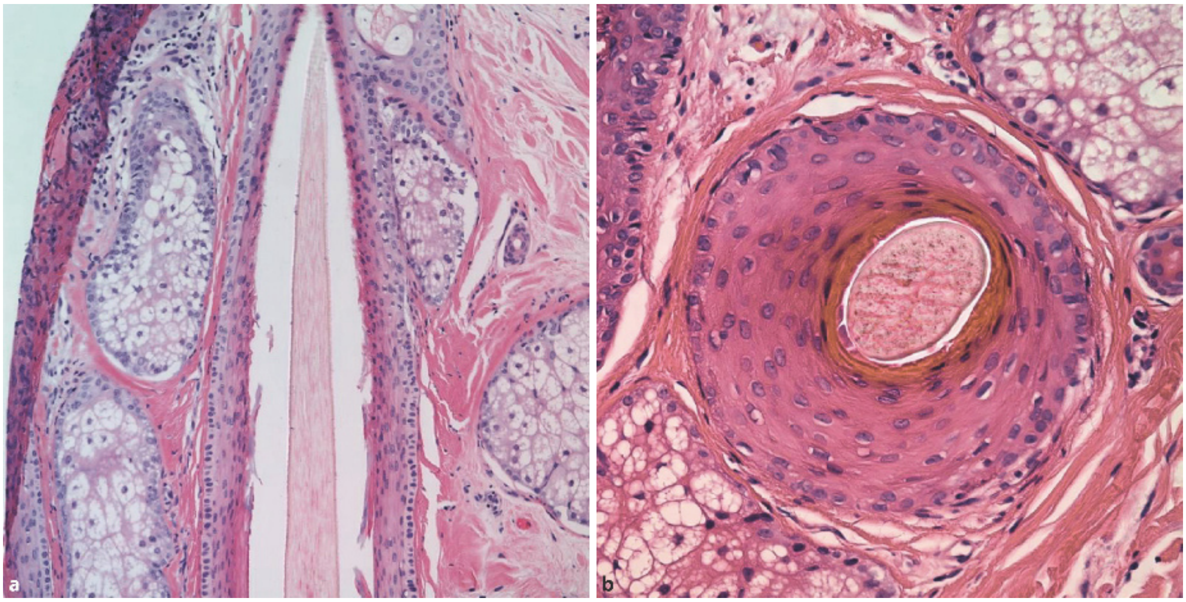


Fig. 7.11 a Upper isthmus, vertical section: follicle lined by outer root sheath and trichilemmal keratin, with some residual disintegrating inner root sheath in lower part of section (hematoxylin and eosin stain, original magnification 200×). **b** Upper isthmus, horizontal section: the outer root sheath or trichilemma is lined by trichilemmal keratin (hematoxylin and eosin stain, original magnification 400×)

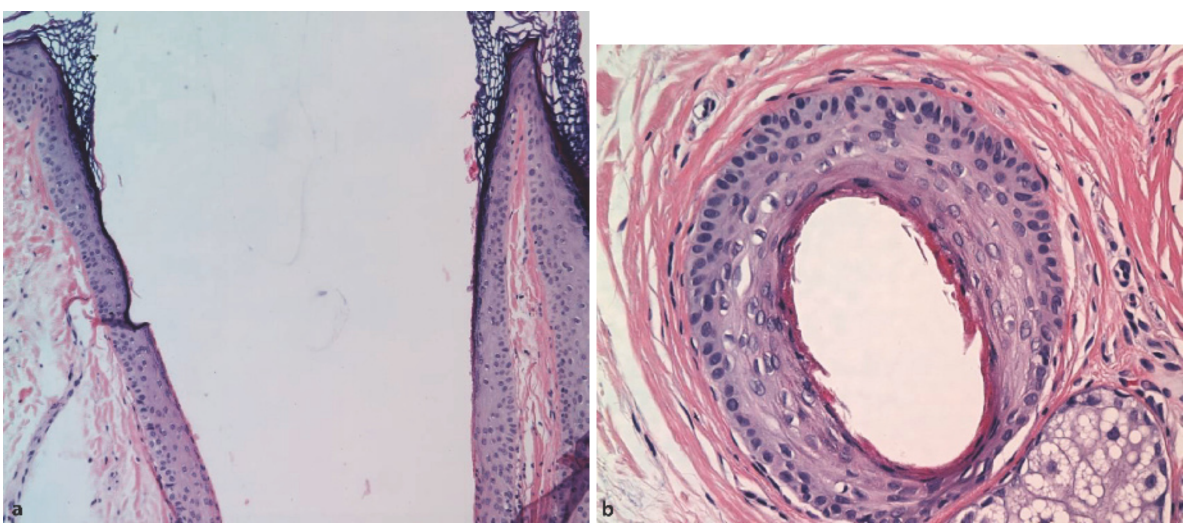


Fig. 7.12 **a** Infundibulum, vertical section: the dilating follicular opening is surrounded by external root sheath lined by skin surface epidermis with granular layer and basket weave keratin (hematoxylin and eosin stain, original magnification 200×). **b** Infundibulum, horizontal section: external root sheath is lined with skin surface epidermis with a granular layer (hematoxylin and eosin stain, original magnification 400×)

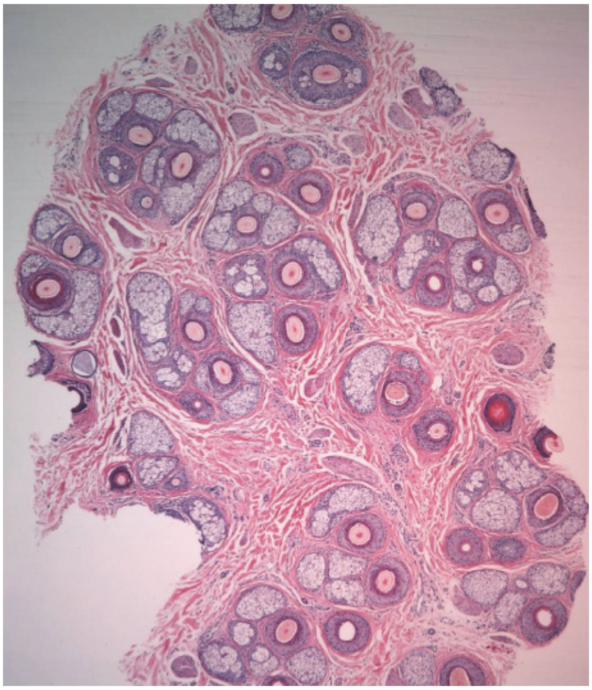


Fig. 7.13 Follicular units, horizontal section at upper isthmus level: somewhat hexagonal packets of terminal and vellus hair, sebaceous glands and ducts and arrector pili muscles, enclosed in loose collagen, are seen. These represent follicular grouping at the skin surface (hematoxylin and eosin stain, original magnification 40×)

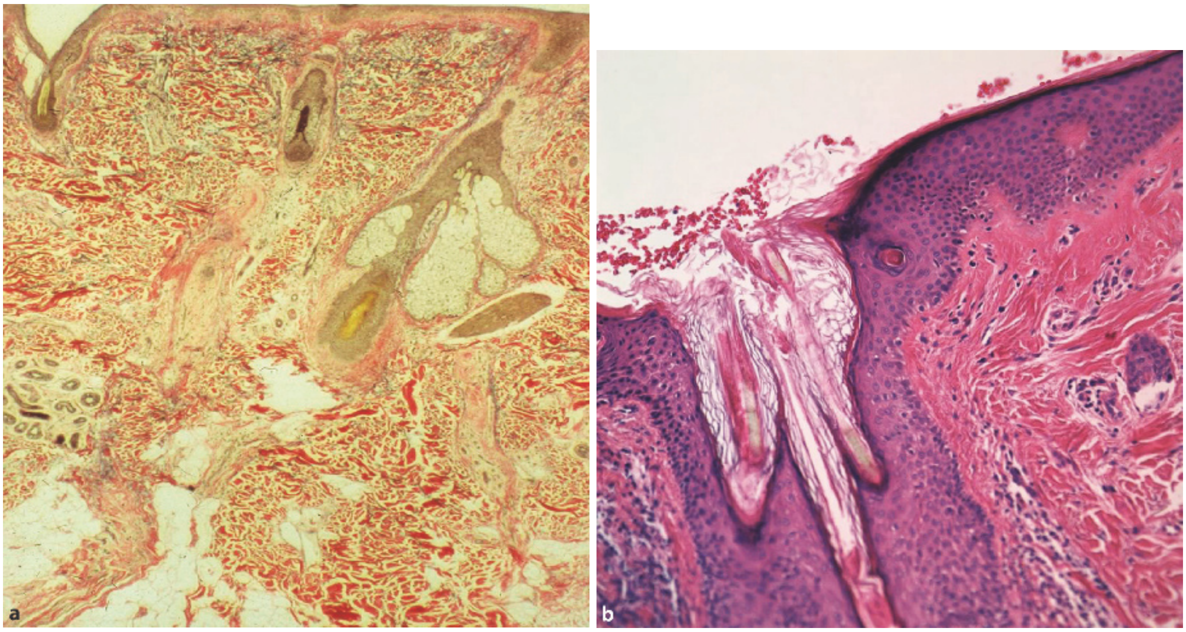


Fig. 7.14 **a** Vellus hair, vertical section, upper and mid dermis: one vellus hair follicle is rooted in papillary dermis below a dilated infundibulum. One vellus-like hair follicle is rooted in upper dermis, but is attached to an underlying streamer (stela) extending down to reticular dermis, implying miniaturization of a terminal hair follicle. The third follicle shows a terminal hair in telogen at the level of insertion of the arrector pili muscle, the so-called bulge area where stem cells are found (Elastic stain, 100×). **b** Vellus hair, vertical section: three vellus hairs are projecting into one follicular infundibulum (hematoxylin and eosin stain, original magnification 200×)

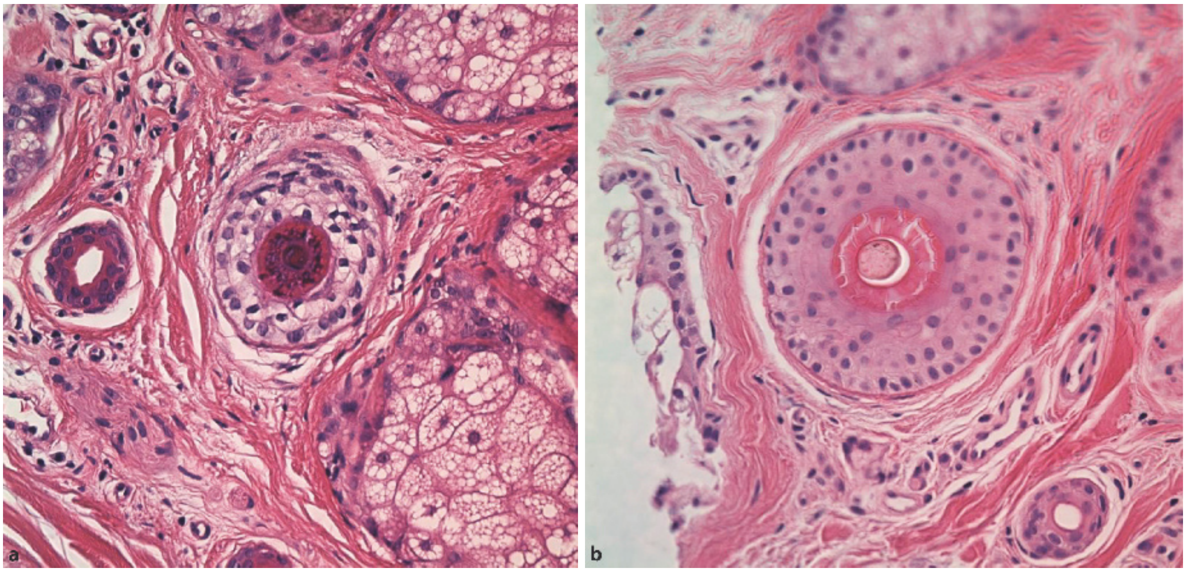


Fig. 7.15 **a** Vellus hair, horizontal section: the central vellus hair shaft has a diameter equal to the thickness of its investing inner root sheath. Its outer root sheath is fairly thin at two to three cell layers. It represents a true vellus hair (hematoxylin and eosin stain, original magnification 400×). **b** Vellus hair, horizontal section: the diameter of the central hair shaft is not much larger than the thickness of its inner root sheath. The outer root sheath is fairly thick at three to five cell layers. This suggests that it is a vellus-like hair, presumably a miniaturized terminal hail (hematoxylin and eosin stain, original magnification 400×)

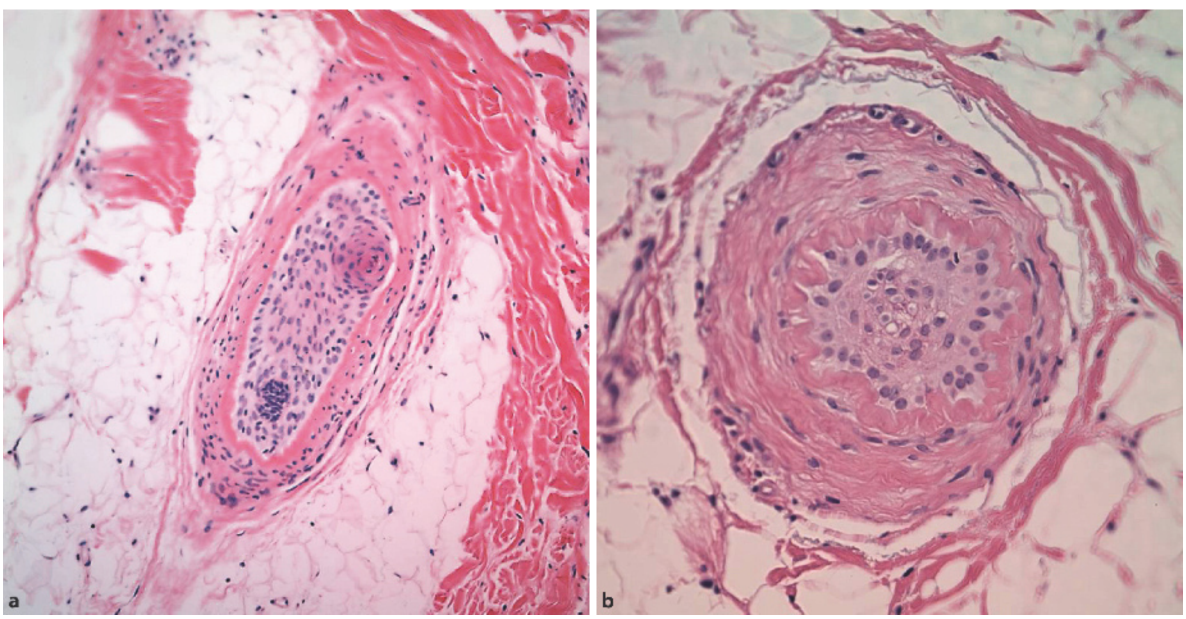


Fig. 7.16 **a** Terminal catagen hair, vertical section: the underlying streamer indicates that this terminal hair rooted in subcutaneous fat is retreating up the follicle. The level of this section shows only a shrinking outer root sheath (trichilemma), which is surrounded by a thickened hyaline membrane indicating catagen (hematoxylin and eosin stain, original magnification 200×). **b** Terminal catagen hair, horizontal section: the hair shaft and inner root sheath have ascended above the level of this section, which shows central trichilemmal shrinkage, surrounded by a thickened, convoluted hyaline membrane indicating catagen (hematoxylin and eosin stain, original magnification 400×)

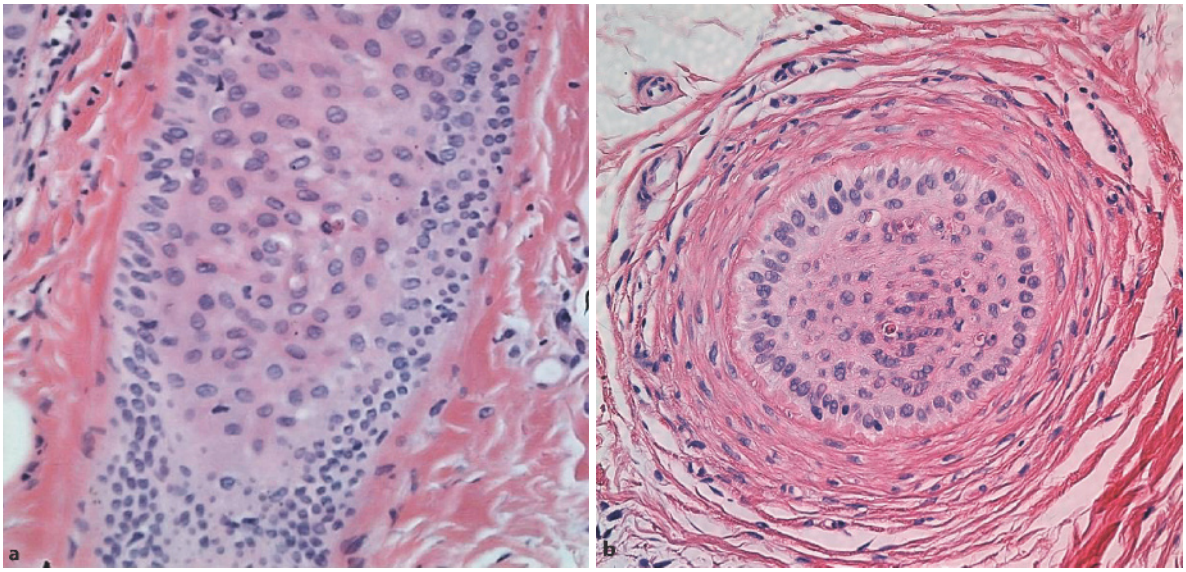


Fig. 7.17 **a** Terminal catagen hair, vertical section: a shrinking trichilemma, with central single cell apoptosis, with surrounding thickening of the hyaline membrane indicates a catagen follicle (hematoxylin and eosin stain, original magnification 400×). **b** Terminal catagen hair, horizontal section: a shrunken trichilemma, below the level of the hair shaft and inner root sheath above it, shows individual cell apoptosis, and is surrounded by a well-defined hyaline membrane and compensatory thickening of the dermal sheath (hematoxylin and eosin stain, original magnification 400×)

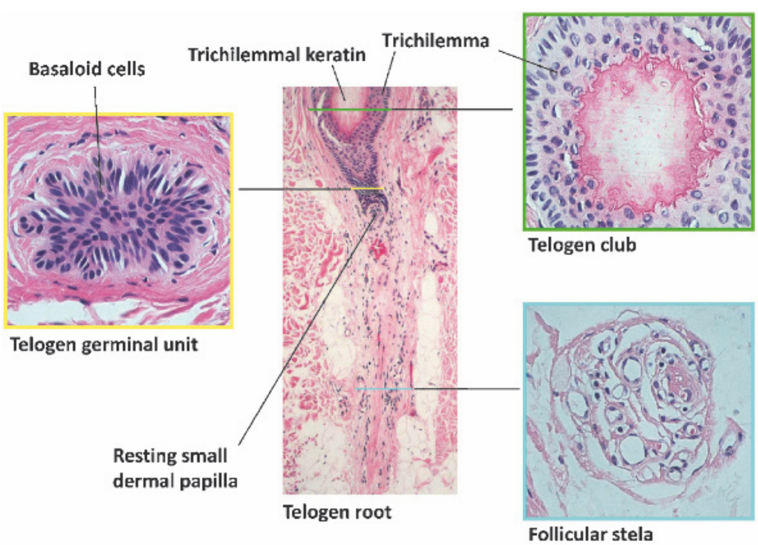
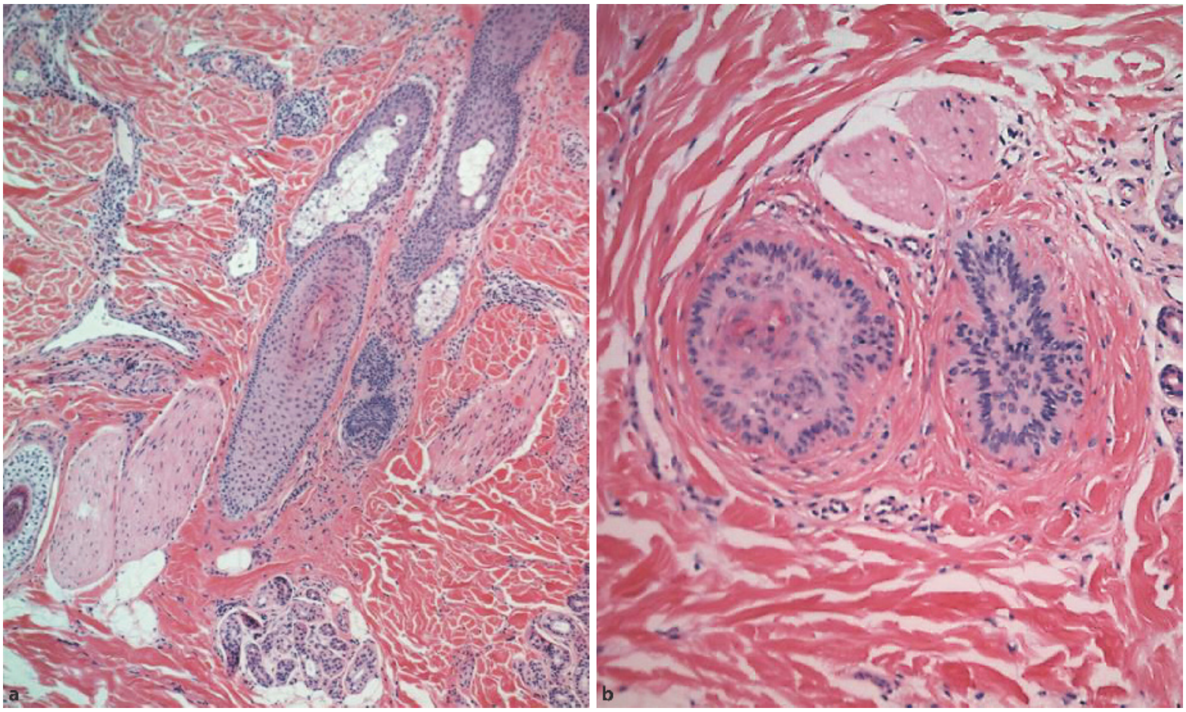


Fig. 7.18 The central panel in vertical section shows the resting telogen hair below the point where the clubbed hair shaft root is situated. The red bulge is the sac of trichilemmal keratin which cushions the root. The vestigial hair bulb and dermal papilla are hanging below, trailing the follicular streamer (angiofibrotic track or stela) which indicates the up and down pathway for the cycling hair. The three horizontal sections indicate the features of the telogen hair club, the telogen germinal unit and the follicular stela. Reprinted from [12] with permission from Canfield Publishing

7.6.6.2 Terminal Telogen Hair

As the hair follicle enters telogen, it retracts to the level of the bulge at the site of insertion of the arrector pili muscle into the follicle (Fig. 7.18). Here the resting hair comprises a telogen germinal unit situated below the telogen club. The telogen germinal unit consists of trichilemma, which is somewhat convoluted and surrounded by palisading basaloid cells. The telogen germinal unit has a characteristic appearance and shows no obvious apoptosis (Fig. 7.19) [3]. A telogen club comprises a central mass of trichilemmal keratin, star-shaped in



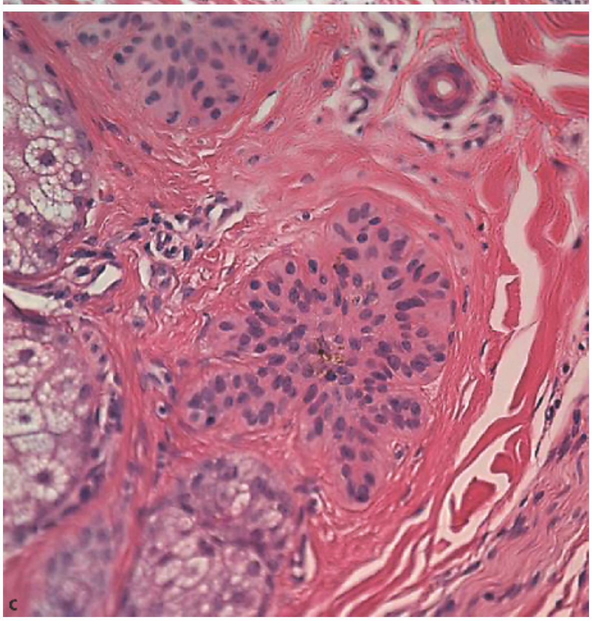


Fig. 7.19 **a** Telogen germinal unit, vertical section: basaloid cell islands with palisaded borders below the upwardly retreating follicle indicate telogen germinal unit (hematoxylin and eosin stain, original magnification 100×). **b,c** Telogen germinal unit, horizontal section: different configurations of telogen germinal units are shown here (hematoxylin and eosin stain, original magnification 100×)

horizontal section, surrounded by trichilemmal and fibrous sheaths, connecting telogen germinal units and hair shafts (Fig. 7.20a,b). The recognition of terminal, anagen, catagen, and telogen hairs is only possible from the examination of the lower follicle below the bulge level for the presence of inner root sheath, apoptosis, or trichilemmal club, respectively. In the upper follicle, only a keratinized hair shaft can be seen with no internal root sheath, so discrimination between anagen, catagen, or telogen hairs is not possible at this level.

After 2–4 months of telogen, a new anagen hair bulb deelops from dermal papilla beneath the telogen germinal units and grows down the existing follicular tract or stela (Fig. 7.20c) to form an anagen hair. Subsequent hair cycling will continue throughout life for as long as the hair follicle is viable.

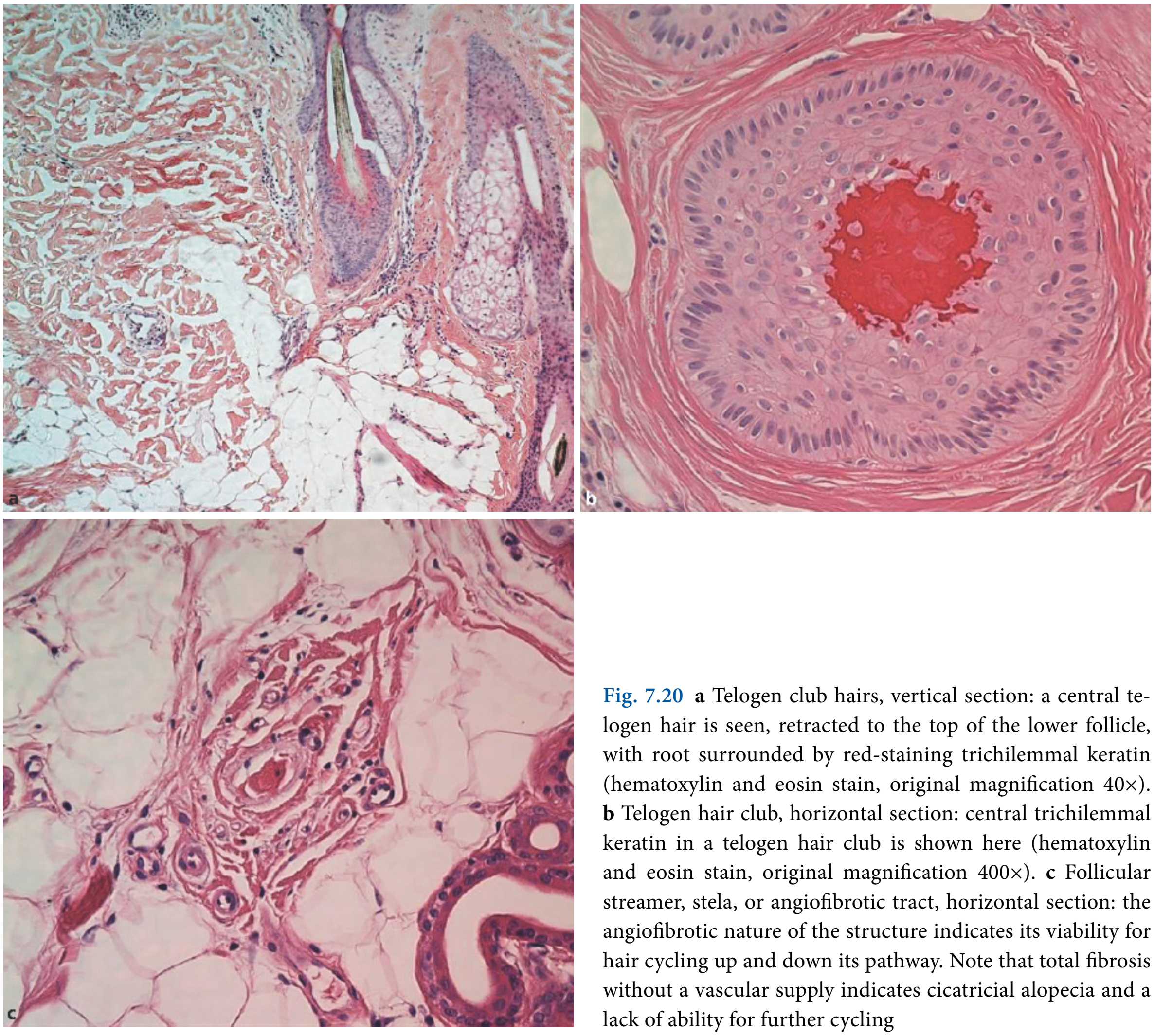


Fig. 7.20 **a** Telogen club hairs, vertical section: a central telogen hair is seen, retracted to the top of the lower follicle, with root surrounded by red-staining trichilemmal keratin (hematoxylin and eosin stain, original magnification 40×). **b** Telogen hair club, horizontal section: central trichilemmal keratin in a telogen hair club is shown here (hematoxylin and eosin stain, original magnification 400×). **c** Follicular streamer, stela, or angiofibrotic tract, horizontal section: the angiofibrotic nature of the structure indicates its viability for hair cycling up and down its pathway. Note that total fibrosis without a vascular supply indicates cicatricial alopecia and a lack of ability for further cycling

7.6.7 Follicular Counts and Image Analysis

Horizontal sections of scalp biopsy samples provide an accurate method for counting, typing, and sizing hair follicles [11]. The information gained is reproducible by different observers and by various methods of image analysis. Data of statistical significance can be produced for diagnostic, investigational, and therapeutic purposes [13, 14]. Upper and lower sections of a 4-mm scalp biopsy can be marked for image analysis (Fig. 7.21).

7.7 Experimental Techniques

Accurate, detailed follicular counts of hair follicles are easily obtainable in horizontal sections and are useful for diagnosing and evaluating the effects of treatment.

Image analysis of hair follicles in horizontal sections is useful for measuring changes in hair shaft numbers and diameters in drug studies.

Special stains may also be valuable in the diagnosis and research of hair disorders.

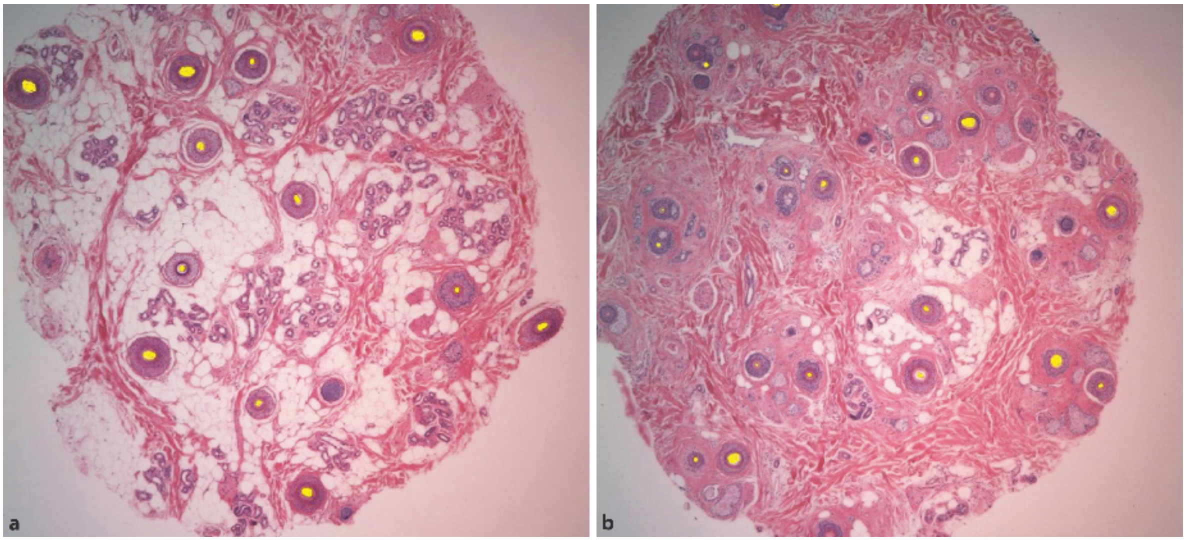


Fig. 7.21 Follicular counts and image analysis: horizontal sections of 4-mm punch biopsy samples through reticular (**a**) or papillary (**b**) dermis are easily utilized for clinical and investigational studies. Reprinted from [12] with permission from Canfield Publishing

7.8 Clinical Relevance

An understanding of the normal anatomy of the hair follicle is needed to diagnose and research hair follicle disease under the microscope and in order to effectively treat hair disorders.

7.9 Outlook – Future Developments

Future studies of normal and abnormal hair structure and function will lead to therapeutic advances in hair disease.

Summary for the Clinician

It is important for clinicians to recognize the microscopic appearances of normal cycling human hair follicles. This is achieved in the first instance by taking a full-thickness, 4-mm punch biopsy of the scalp. Subsequently vertical and horizontal sections may be needed for three-dimensional evaluation. Follicular changes in anagen, catagen, and telogen need to be recognized. Follicular counts in horizontal sections are valuable in the diagnosis and treatment of hair disorders, especially the noncicatricial alopecias

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Chapter 8

Hair Growth Assessment Techniques

Ulrike Blume-Peytavi, Kathrin Hillmann, Marcella Guarrera

8

Synonyms

hair diagnostic tools, hair growth measurement

Key Features

- Qualitative and quantitative methods are essential for objectively evaluating hair growth activity.
- Standardized techniques are mandatory for clinical studies and for evaluating agents that inhibit or promote hair growth.
- Hair density, hair width, and global photography evaluation are generally accepted parameters for judging hair volume, hair growth, and hair loss.
- For daily practice and individual trichologic follow-up, videodermoscopy, pull test, TrichoScan and in selected cases scalp biopsy are helpful tools.

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8

8.1 Introduction

Hair is a major esthetic display feature of the human body, especially in social and sexual interactions. Diagnosis of hair diseases occurred as early as ancient Egyptian times and is one of the oldest medical disciplines. Today, hair loss or thinning, and hypertrichosis or hirsutism are common complaints in clinical dermatology, but patients seeking advice for their hair problem are not necessarily completely bald or overall haired. The difficult task in diagnosing hair and hair disorders is to distinguish between a true disorder and a subjective complaint and to analyze the underlying pathogenesis. Patients consult for focal or diffuse effluvium, non-scarring or scarring alopecia, changes in hair structure or color and hair graying. Establishing the correct diagnosis is the key feature of successfully managing a hair patient.

Evaluation of scalp hair requires objective techniques that are sensitive enough to assess fundamental variables such as hair quality (density, elasticity, strength, fragility), fiber diameter, proportion of actively growing hair, and linear growth rate, and to distinguish hair shaft anomalies. Such information provides essential details for determining normal morphology, for understanding changes arising from disease, and for developing adequate treatment.

Hair diagnostic tools in a trichologic consultation comprise a thorough clinical history, a physical examination including scalp and body hair distribution, videodermoscopy, pull test, and microscopic hair shaft examination. In selected cases a scalp biopsy may be necessary. Clinical studies need sensitive tools for monitoring hair loss and especially for objectively evaluating the response to treatment. Such methods must be able to analyze biological parameters of hair growth, such as total hair density, terminal and vellus hair density, hair shaft thickness and, if possible, hair growth rate. In addition, increased hair growth, as well as hair structure defects, whether of genetic origin or cosmetically induced, need reliable analysis techniques.

8.2 History

Numerous methods have been reported [3, 91] to assess the rate of hair growth. The techniques can be classified as invasive (e.g., biopsies [40, 90]), semi-invasive (trichogram [8, 53], unit area trichogram [69]) or non-invasive {e.g., global hair counts [16] and phototrichogram (PTG) methods [12, 28, 32, 72, 86, 88]}. Quantitative methods for the analysis of human hair growth and hair loss are necessary to determine the efficacy of hair-promoting drugs.

As early as 1964 Barman et al. [1] reported a method using optical contact microscopy to calculate hair growth parameters, and much later Hayashi et al. [39] described a similar approach for the measurement of hair growth by the use of optical microscopy and computer analysis. However, these authors were unable to automate the process of calculation and measured the thickness of hairs visually with the cursor on the computer monitor. A very similar approach has been tested with the use of the PTG. The PTG has proven to be a suitable and non-invasive tool to monitor the hair growth phases in vivo. This technique was improved by image analysis [86] and later by immersion oil and digital contrast enhancement [87]. Until recently image analysis was a tedious and time-consuming process. Unsuccessful attempts to automate the process have been made several times [39, 60, 87]. The poor success was mainly because the hair follicles (HF) on the scalp grow in groups (de Meijieres trio groups) rather than singly and therefore neighboring HF typically overlap or may be aligned in parallel. Furthermore, any photographic analysis software needs good contrast between the HF and the scalp skin to be analyzed, and the fact that many hairs lose their natural pigmentation due to aging or androgenetic alopecia (AGA) makes them much more difficult to detect.

8.3 Hair Measurement Scores

Hair growth assessment is based on the clinical experience and trichological knowledge of the examiner. Careful clinical examination is mandatory in order to establish the differential diagnoses, which will then inform the choice of assessment technology made. The clinical examination implies scalp and body hair distribution. Scalp examination has to be performed in three stages. First inspect the scalp for inflammation, scaling, erythema, and follicular openings. It is important to differentiate firstly between non-scarring and scarring alopecia, and whether visible follicular units and openings are present; scarring alopecias are devoid of follicular units. Second, examine the distribution pattern and density of hair. Third step: study the quality of the hair shaft in terms of caliber, fragility, length, and shape [76].

The use of precise and reproducible scoring systems for scalp and body hair by the physician is best approached by comparison with available scores determined for different conditions.

8.3.1 Scalp Hair Distribution

The scalp hair classification method that has the broadest spectrum is that for AGA. The ones with most widespread use globally are those described by Hamilton-Norwood and Ludwig described in Chaps 9 and 10 [49]. However, reports on scalp hair assessment scores for investigating pattern hair loss are numerous (Table 8.1) [13, 57].

Recently a classification for assessing the extent of alopecia areata (AA) was proposed in order to enable it to be standardized for clinical study purposes (Fig. 8.1).

8.3.2 Body Hair Distribution

A scoring system for body hair growth should differentiate between hypertrichosis and hirsutism and should rate the degree of hirsutism. In addition the scoring system used should help the follow-up of the course of hirsutism under treatment regimens (Table 8.2).

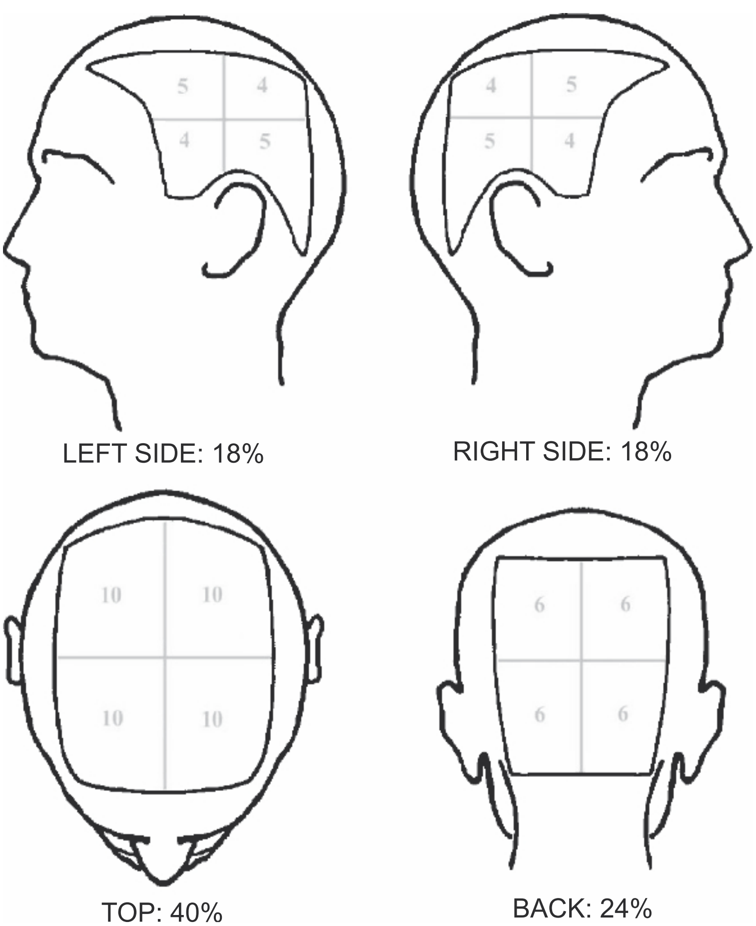


Fig. 8.1 Visual aid (Olsen/Canfield) for estimating percentage scalp hair loss, "x" score and percent regrowth. Using this diagram, one can determine the percent scalp hair loss in a given quadrant and multiply this by the total scalp area delineated by that quadrant and sum the resultant numbers for each quadrant to give the total percent scalp hair loss. This diagram also allows the evaluator to graph the area(s) of alopecia, if desired, in order to facilitate the estimate of percent scalp hair loss and to compare the hair loss on subsequent evaluations [58]

Table 8.1 Historic overview on scalp hair assessment scores in pattern hair loss

Year	Investigators	Classification
1950	Beek [4]	Intensity and extent of scalp and body hair growth in 2000 Caucasian men and women are compared. The results are used to assess influences of hormone secretion, puberty, and climacteric on hair growth and to define virilism and hirsutism
1951	Hamilton [37]	Classification of male pattern baldness based on the description of eight evolutive aspects and three subgroups and further comparison of the incidence of baldness for Caucasians and Chinese. In 1975 Norwood took this classification up and made a more detailed description of male pattern baldness
1953	Ogata [56]	Fifteen shapes of balding are distinguished into six types of hair loss with the potential for grading into early, intermediate and late type
1969	Feit [25]	A more detailed classification than Hamilton's 1951 version. Characterization of 12 different varieties of 16 categorized aspects
1970	Setty [74]	A simplified three-group version of Hamilton's version including hair loss in black people. Totopilosis (relates to Hamilton type I), indentato-pilosis (Hamilton type II-V) and indentatocirculo-pilosis (more or less Hamilton VI-VII; confluent/nonconfluent)
1972	Ebling and Rook [23]	Classification which differentiates alopecia into five degrees: for grades I–III medical treatment is appropriate; for grade IV, surgical therapy; for grade V, no solution is available
1975	Rook and Dawber [66]	A classification of five evolving stages
1975	Norwood [54]	Hamilton-Norwood classification (see Chap 9, Fig. 9.4)
1976	Bouhanna and Nataf [14]	Bouhanna developed a simplified classification in three stages of evolution with or without vertex balding
1977	Ludwig [51]	Ludwig classification (see Chap 10, Fig. 10.1)
1984	Blanchard and Blanchard [6]	Classification distributed into five stages of evolution by measuring the distance of fixed landmarks with the borders of alopecia
1988	Camacho [15]	A classification of AGA which involves the hair loss pattern. Male AGA (MAGA.I-V) and male pattern female AGA (FAGA.M.I-V) is judged with the Ebling classification. Female AGA (FAGA.I-III) and female pattern male AGA (MAGA.F.I-III) are rated with the Ludwig classification
1992	Savin [73]	The Savin scale is a photographic depiction of gradations of scalp hair loss in women as determined by parting width. The patient's hair is compared with eight computer-generated pictorial representations of the central scalp hair parted in the middle
2000	Bouhanna [13]	A pre-surgical method to determine the extent of bald and hairy areas, measured by five distances on the scalp: median sagittal distance, left and right paramedian distances, transverse supra-auricular distance, temporal anterior spacing distance
2004	Olsen et al. [58]	The scalp is divided in four regions: frontal (F), bitemporal (T), midscalp (M), and vertex (V). These regions are each assigned a 7-point density scale of 0 to 6, with 0 being no loss and 6 being total or near-total terminal hair loss

Table 8.2 Historic overview on body hair evaluation scores [2]

Investigators	Number of sites evaluated	Specific feature evaluated
Pedersen (1943) [59]	12	Presence of hair at each site but no quantitative assessment
Beek (1950) [4]	19	Presence of hair at each site but no quantitative assessment
Garn (1951) [30]	11	Patterns of hair growth at each site and form of hair shaft present (e.g., curly or straight). No quantitative assessment
Shah (1957) [75]	9	Quantitative assessment of terminal hairs >0.5 cm: quality (*Q;* scored 1–3), density (*D;* 0–3), proportion of zone covered with hair (*P;* 0–1), giving a total score (*Q*×*D*×*P*)
Ferriman and Gallwey (1961) [26]	11	Quantitative score based upon distribution of hair on each site (see Fig. 8.2)
Lorenzo (1970) [50]	7	Quantitative score based upon density and extent of involvement
Hatch et al. (1981) [38]	9	Quantitative score based on distribution of hair on each site
Lunde (1984) [52]	18	Quantitative assessment of length and density of terminal hairs >0.5 cm

8.3.2.1 Ferriman and Gallwey Score

8.3.2.1.1 Introduction

The Ferriman–Gallwey scoring system is an easily and the most widely used tool for the evaluation and quantification of hirsutism in women. It was developed by Ferriman and Gallwey in 1961 for anthropological research [26]. Today the modified Ferriman–Gallwey score (mFG) evaluates nine regions for their degree and nature of body hair growth from 0 to 4. On the basis of a draft scale the body regions are compared and a score above 8 is a strong sign for hirsutism. It is not applicable in Asia due to ethnical variation in hair growth.

8.3.2.1.2 Technology

8.3.2.1.2.1 Indication

Excessive facial and body hair growth with male pattern distribution in women is indicative of hirsutism, who require a semi-quantitative method to estimate their hair growth intensity and for follow-up under therapy.

8.3.2.1.2.2 Technical Procedure

For the original Ferriman-Gallwey score 11 body regions are rated from 0 (absence of terminal hair) to 4 (very distinctive terminal hair growth). The sites are: upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, arm, forearm, thigh, and leg (Fig. 8.2).
Today, a mFG score rating only nine regions, leaving leg and forearm unconsidered, is the most frequently used evaluation method. This score evaluates excessive hair growth with a male pattern. All nine face and body regions are judged with a score of 0–4 and all points are summed; today in daily practice a score >6, in certain countries >8, is considered as hirsutism. However, there is no standard value that defines a threshold for hirsutism. Ferriman and Gallwey took a sum of above 5 as representative for abnormal hair growth and a valuable indicator of hirsutism [20]. Other studies took scores of between 6 [77] and 10.

The Abraham's classification stages a patient's degree of hirsutism (see Chap 17, Table 17.1).

8.3.2.1.2.3 Complications

To confidently establish observer conformity is difficult, due both to the lack of method standardization [2] and the fact that most patients have epilated, waxed, shaved or used other techniques to remove their hair before their consultation, meaning that the clinician cannot rate them correctly by face and body examination. However, Hahn et al. [36] report rather good reproducibility and reliability when patients self-evaluate.

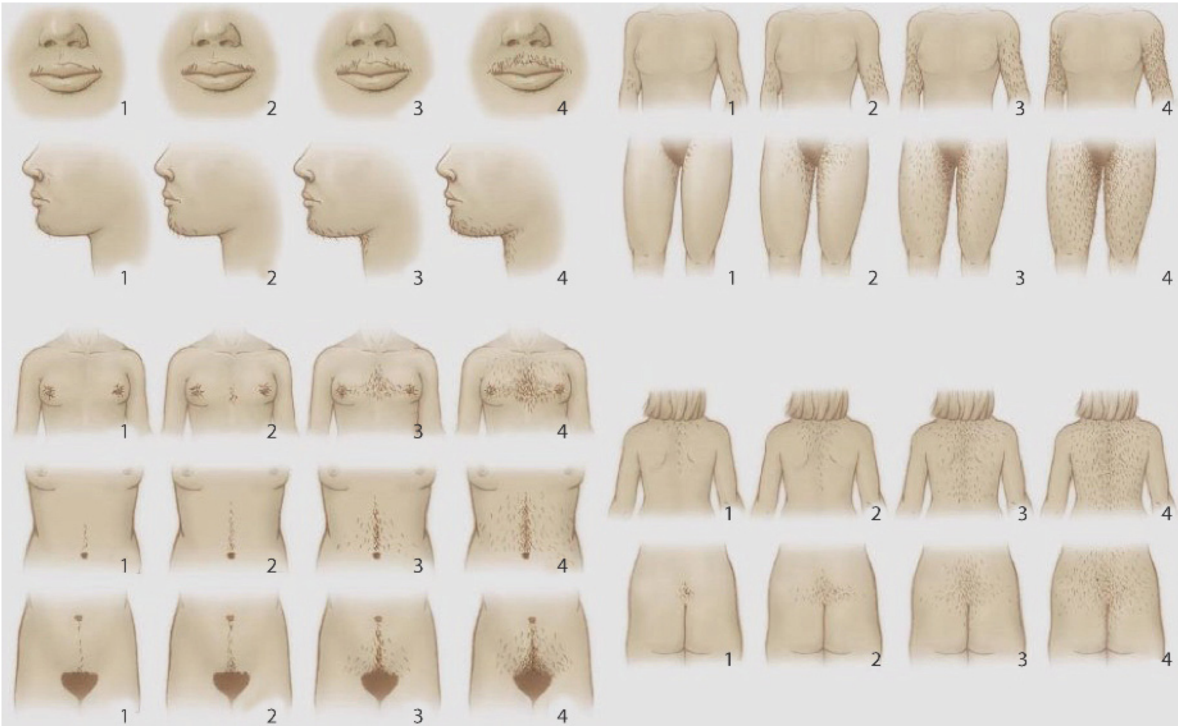


Fig. 8.2 Modified Ferriman-Gallwey score (mF6) [67]: Nine body regions are evaluated for their degree of hair growth from 0–4. A total score >8 is a sign for hirsutism

8.3.2.1.2.4 Combination Possibilities and Practical Advice

The mFG can be combined with photographic documentation and a phototrichogram or TrichoScan in clinical studies. The mFG score can be used to evaluate the severity of hirsutism and to follow-up the hair growth activity under different therapeutic regimens.

8.4 Hair Growth

8.4.1 Hair Pull Test

8.4.1.1 Introduction

The hair pull test is a simple test for the clinician to determine the ongoing activity and severity of any kind of hair loss. The pull test technique shows rather high interexaminer variability; however, each examiner standardizes his or her own procedure and has benchmarks for assessing patients.

8.4.1.2 Technology

8.4.1.2.1 Indication

The pull test helps to roughly estimate the severity of hair loss in daily practice with a high interobserver variability. Its range of application in the diagnostic process reaches from androgenetic alopecia and alopecia areata, to diffuse effluvium, to scarring alopecia.

8.4.1.2.2 Technical Procedure

A bundle of about 50–60 hairs is grasped between the thumb, index finger, and middle finger from the base near the scalp. The hair is firmly, but not forcibly, tugged away from the scalp as fingers slide along the hair shaft [76]. Another procedure is to use both hands, and grasp a tuft of hair between two fingers of one hand and pull at it with the other [33].

Afterwards the number of extracted hairs is counted and, depending on the diagnosis, sometimes examined under the microscope, e.g., in loose anagen hair.

If more than 10% of grasped hairs, or six hairs, are pulled away from the scalp, this constitutes a positive

pull test and implies active hair shedding. If fewer than six hairs can be easily pulled out, this is considered normal physiologic shedding [76].

The same procedure is repeated in four scalp areas (right + left parietal and frontal + occipital areas). To standardize the test and to obtain comparable results, patients are asked to refrain from washing their hair in the 5 days before the examination; however, some clinicians have a standard 2-day period between shampooing and the pull test, although it is important that they make this clear when reporting the results. The pull test is normally negative on the day of shampooing as all telogen hairs have been rinsed away.

Despite these requests, most patients come to the office having just shampooed their hair, or they do not adhere to the guidance on the interval from the last shampooing required (Fig. 8.3a,b) (Table 8.3).

8.4.1.2.3 Complications

Discrepancies may arise because of differences in pulling strength, and in the density or thickness of hair shafts. The pull test is a very rough method and difficult to standardize, as it is subject to high interindividual variation among investigators. The pulling force is not distributed uniformly all over the whole hair bundle, which creates variation from one hair to another. It seems to be useful only in acute phases of hair loss in the more severe conditions [83].

Table 8.3 Pull test (*PT*) results and the corresponding hair disease [76, 78, 90]

Disease	Hair pull test
Normal	0–5 hairs can be pulled; a test with ≥6 hairs is positive
Alopecia areata	Positive, ≥6 hairs on light microscopy show dystrophic anagen and telogen stage
Androgenetic alopecia	Mostly normal. In active AGA, positive on the top of the scalp; negative in occipital area
Acute anagen or telogen effluvium	Positive in active phases with increased numbers of anagen or anagen dysplastic hairs or normal telogen hairs
Chronic telogen effluvium (CTE)	Positive only in active phase of CTE always with 6–8 telogen roots when examined with light microscopy
Trichotillomania	Negative with no pluckable hairs
Loose anagen syndrome	Highly positive; up to 100% when hairs are examined under the microscope; anagen hair root mostly lacking the hair sheath (anagen dysplastic)

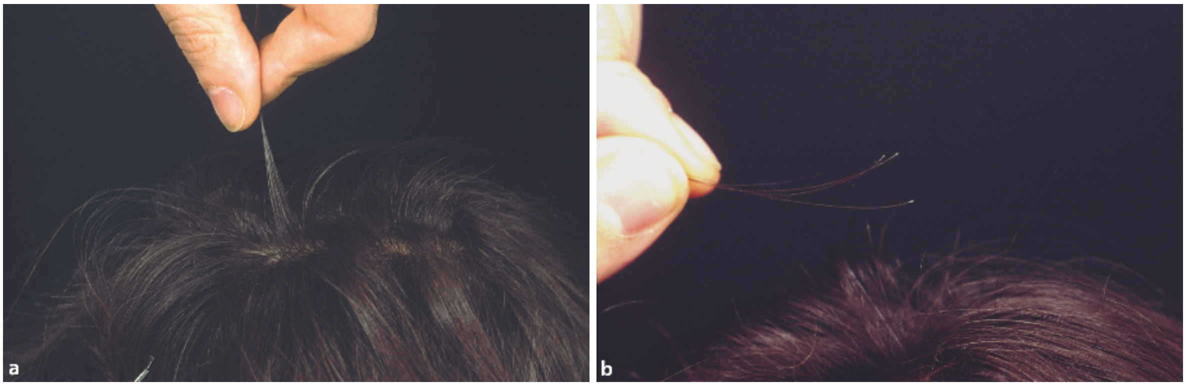


Fig. 8.3a,b A bundle of hairs is grasped between two fingers. A constant traction force in the direction of hair growth is used to pull out slightly adhered hairs from the hair follicles

8.4.1.2.4 Combination Possibilities and Practical Advice

The hairs that are pulled out can be analyzed by light microscopy to narrow the differential diagnosis. The pull test is only a rough approach to diagnosis and can be used during the trichological examination. However, more reliable tests and objective measurements should be added where necessary.

The hair pull test seems to be useful for the practitioner for diagnosis and therapeutic follow-up; however, it is not suitable for use in clinical studies.

If the same investigator always uses the pull test in the same way, it is useful for him or her when routinely used in patient follow-up.

8.4.2 Wash Test (Modified)

8.4.2.1 Introduction

The wash test was first introduced to quantify the amount of hair lost under standardized washing conditions. It is a non-invasive method to measure hair loss by counting and identifying rinsed out hairs.

The wash test was modified by Rebora et al. [65] as the so-called AGA/TE wash test in order to distinguish between AGA and telogen effluvium (TE), by counting the number of vellus and terminal telogen hairs rinsed out on washing.

8.4.2.2 Technology

8.4.2.2.1 Indication

The modified AGA/TE wash test is used to measure the severity of hair loss in TE or AGA.

8.4.2.2.2 Technical Procedure

After a 5-day abstention from shampooing, the patients wash and rinse their hair in a basin whose hole is covered by gauze to entrap the lost hairs. Hairs are then collected in a paper envelope and brought to the examiner for hair count and further analyses.

For the AGA/TE modified wash test, the hairs are counted and divided into three classes of hair length: (1) long hair >5 cm, (2) intermediate hair (>3 to <5 cm), (3) short vellus hair (<3 cm). Hairs shorter than 3 cm are counted as telogen vellus hairs.

The final results of the AGA/TE modified wash test are given as the total number of telogen hairs and the percentage of telogen vellus hairs.

8.4.2.2.3 Complications

The amount of shampoo and water used and the duration and strength of the massage are very difficult to standardize [33]. The standard error may be rather high when there is high rate of hair breakage, leading to double counting of broken hairs, or when anagen hairs break during the washing procedure.

Another disadvantage is that the AGA/TE wash test cannot be used in patients with very short hairs, and in women with curly hairs in whom lost hairs tend to be retained. Counting may be rather time consuming when there is a large quantity of hairs.

8.4.2.2.4 Combination Possibilities and Practical Advice

To avoid counting anagen or broken hair for the AGA/TE test, and for a precise diagnosis the counted hairs should be examined microscopically for hair cycle phase differentiation, shaft abnormalities, and the morphologic appearance of the distal tip.

The normal average daily loss of hair ranges between 30 and 70 hairs, going up to as much as 200–250 on the day of shampooing, if not performed daily. When more than 70 hairs are shed daily, a true pathological condition is probably present [61], however only continuously elevated shedding rates will lead to alopecia.

The results of the AGA/TE wash test suggest four possible diagnoses (Fig. 8.4).

8.4.3 Hair Weighing

8.4.3.1 Introduction

The efficacy of agents that promote hair growth can be established by comparing the total hair weight and counting grown hair in a small, carefully standardized scalp area [61]. In the beginning hair weighing methods were used to verify hair growth in test animals, but in 1990 Price [63] defined a standard protocol for measuring hair weight in humans, which was subsequently used in clinical trials.

8.4.3.2 Technology

8.4.3.2.1 Indication

Hair weighing can be used in clinical studies to evaluate and analyze the effect of topically or systemically applied drugs or cosmetic molecules.

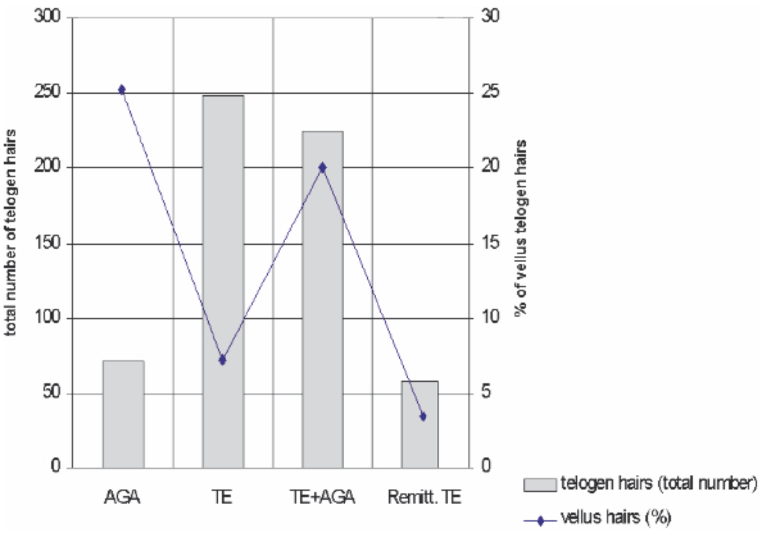


Fig. 8.4 The *columns* indicate the total number of telogen hairs lost during the shampooing and rinsing, while the *line* shows the percentage of vellus (hair shaft less than 3 cm long). The *first column* indicates androgenetic alopecia (*AGA*), the second telogen effluvium (*TE*), the third the androgenetic alopecia-telogen effluvium association (*TE+AGA*), the last remitting telogen effluvium (*Remitt TE*)

8.4.3.2.2 Technical Procedure

On a well-defined site, mostly in the fronto-parietal region, a 1.34-cm^2 area is shaved using a clear plastic template. The site is outlined and later permanently marked by two mini tattoos in nonadjacent corners of the square.

For initial screening hairs are clipped to a length of 1 mm with scissors. After a treatment-free period (4–24 months depending on the expected effectiveness of hair growth promotion) hairs are hand-clipped short under magnification and collected carefully (baseline growth value over a defined period). In the subsequent treatment period hairs are allowed to grow for the same time again as during the screening period, before being clipped and collected. At the end of the study hairs of all sampling periods are degreased and weighed consecutively by an experienced technician separately [63, 64].

8.4.3.2.3 Complications

Hair weighing is a time-consuming method but when the entire analysis is performed by an excellently trained technician responsible for the whole study, good reproducible results can be obtained in monocenter studies. No immediate measurements results are available, as the weighing of all samples is performed at the end of all sampling periods.

The most frequent errors occur during the clipping process, thus this must be carried out most carefully.

8.4.3.2.4 Combination Possibilities and Practical Advice

Combining hair weighing with a hair count and accurate measurement of width and length can be useful [63]. In the future combination with measurement of hair shaft thickness using optical coherence tomography (OCT) may be considered.

Hair weighing is a good diagnostic tool for hair growth evaluation in clinical studies, but not for outpatient monitoring.

8.4.4 Global Photographs

8.4.4.1 Introduction

An increase in hair coverage can be due to an increase in hair density, hair thickness as well as to a continuous increase in hair weight. Thus global photographs are an essential tool in evaluating the overall course of hair volume.

Taking global photographs of hair patients is a standardized method for evaluating hair growth and volume using a stereotactic device with subsequent blinded evaluation by an expert panel comparing photos taken before and after treatment.

The first standardization of global hair photographs for hair growth studies was reported by Lederle in 1987, however it was not until the series of finasteride trials in 1992 that standardized photographs were used successfully as an end point in clinical studies, albeit a secondary one [57].

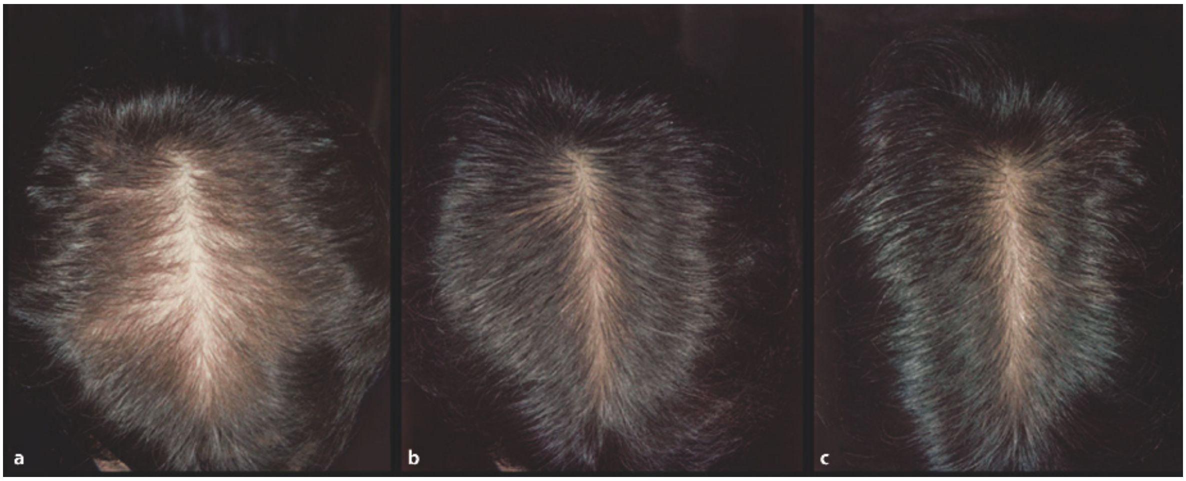


Fig. 8.5a–c Global photography taken in a clinical study applying minoxidil 2% over 48 weeks: (**a**) baseline, (**b**) after 16 weeks of treatment, (**c**) after 48 weeks of treatment. Clinical outcome was evaluated by blinded expert panel as moderate improvement

8.4.4.2 Technology

8.4.4.2.1 Indication

Global photographs are taken for objectively monitoring hair growth activity and hair quality and volume in clinical trials and for long-term follow-up of hair patients under long-term treatment.

8.4.4.2.2 Technical Procedure

A stereotactic positioning device is used on which the patient's chin and forehead are fixed, and on which a given camera and flash device are mounted, ensuring that the view, magnification, and lighting are the same at consecutive study visits, thus enabling precise follow-up of the same region of interest. The investigator is able to convert the stereotactic camera device to the region of interest with vertex, mid-pattern, frontal, and temporal views [16].

The standardized global photographs are subjected to review by a panel of dermatologists whose reproducibility and interobserver agreement of their assessments are very high [57] (Fig. 8.5).

8.4.4.2.3 Complications

The length, color, shape (straight, wave), and combing of the hair must remain constant during the entire length of the study. Patients' hair should be washed on the morning of photography and no hair products such as mousse, gel, or spray should be used. No water should be applied to the hair during hair preparation for the photograph; oil or water on the hair affect the appearance of hair density when the hair is fine and thin.

8.4.4.2.4 Combination Possibilities and Practical Advice

Global photographs can be combined with any quantitative hair growth method such as a trichogram, phototrichogram, TrichoScan or hair weighing.

8.4.5 Unit Area Trichogram

8.4.5.1 Introduction

The unit area trichogram is a semi-invasive (plucking) quantitative method for scalp hair that estimates three of the four main hair growth parameters: hair follicle density, proportion of anagen fibers, and hair shaft diameter.

8.4.5.2 Technology

8.4.5.2.1 Indication

The unit area trichogram can be used for follow-up of scalp hair changes in a study cohort for observing hair growth cycling, and for monitoring topical or systemic drug effects [69, 70].

8.4.5.2.2 *Technical Procedure*

The unit area trichogram is based on plucking hair in a defined area (usually >30 mm²). The area to be sampled should first be degreased with an acetone:isopropanol (60:40, v:v) mixture to remove surface lipids. The area is identified prior to depilation with a skin marker or a roller ball pen using a template containing a precision-drilled hole. The sample area can be quantitatively measured from an enlarged black and white photograph containing a scale bar or a digital computer image. Single hairs are rapidly epilated in a single smooth action in the direction of growth in order to minimize hair root trauma. Subsequently plucked hairs are mounted on double-sided tape and ordered by length. Microscopic analysis enables differentiation between the hair growth phases and measurement of hair length. Each hair is measured in its largest (major axis) and smallest (minor axis) to determine the hair shaft diameter. The diameter of each hair is assessed at the average of these two dimensions [69].

8.4.5.2.3 *Complications*

The plucking of hair causes certain discomfort for the patient and sufficient regrowth time has to be considered while developing study protocols. Although the unit area trichogram has a high reproducibility it is rather time consuming and is unsuitable for large-scale clinical trials.

8.4.5.2.4 *Combination Possibilities and Practical Advice*

The unit area trichogram can be combined with global photographs and can be carried out regardless of hair color.

8.4.6 Trichogram

8.4.6.1 Introduction

The trichogram is a semi-invasive (plucking) microscopic method for hair root and hair cycle evaluation. The morphological examination of hair roots was developed by Scott et al in 1957, however the description "trichogram" was coined by Pecoraro in 1964, who described further trichometric parameters such as hair shaft diameter, hair growth and telogen rate. The trichogram is based on the hair cycle and quantifies hair follicles in their different growth phases.

8.4.6.2 Technology

8.4.6.2.1 *Indication*

The trichogram technique is used for the diagnosis and differentiation of different hair types, of hair shedding and of alopecia via hair root pattern [10].

8.4.6.2.2 *Technical Procedure*

The hair should not be washed for 5 days prior to plucking. By using a rubber-armed forceps 60–80 hairs are plucked at two specific scalp locations depending on the hair disorder. In AGA, in diffuse effluvium and in loose anagen hair, the first site is 2 cm behind the frontal line and 2 cm from the midline, and the second site is on the occipital region, 2 cm lateral from the protuberans occipitalis [10] (Fig. 8.6). In alopecia areata the first site is at the border of the alopecia patch and the second on the contralateral, clinically unaffected, side. The instrument is closed tightly over the hairs at about 0.5 cm above the scalp and rotated to ensure a firm grasp. With one, quick, forceful pull perpendicular to the scalp and always along the direction of hair growth, hairs are removed. For optimal evaluation results hair bulbs are immediately embedded with their roots on a glass slide in an embedding medium which allows microscopic evaluation later and storage of slides for teaching. If mounted on a glass slide in water or on adhesive tape the trichogram must be examined immediately by microscopy. Hair roots are evaluated under a magnifying lens or a low-power microscope to determine the number of hairs in the different phases of the hair cycle and results are given as a percentage of the total number of plucked hairs [10] (Figs. 8.7, 8.8).



Fig. 8.6 The rubber-armed forceps hold tight neatly on the proximal hair shaft, close to the scalp permits to pluck a tuft of 50–80 hairs [10]

8.4.6.2.3 Complications

Hair plucking causes the patient certain discomfort and when inappropriately done can lead to many dystrophic bulbs and broken hairs with no exploitable results. Although the hair pluck adds information, it is dependent on the ability of the operator. The most critical step is the actual pluck maneuver. The technique is time consuming and needs experienced technicians and examiners. Very curly or African hair may render taking the trichogram nearly impossible.

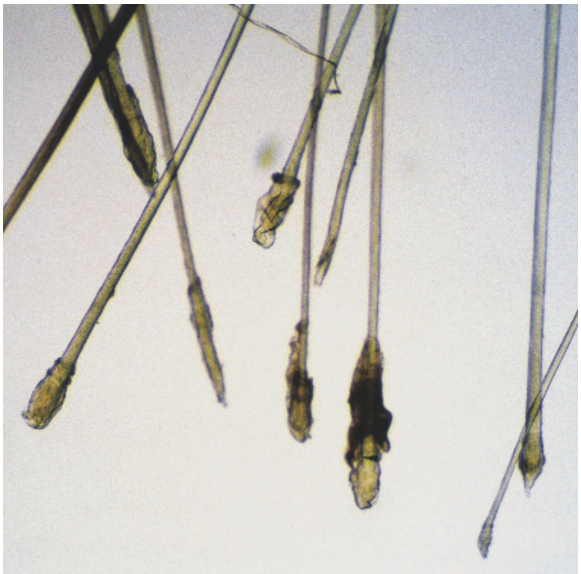


Fig. 8.7 The epilated and embedded hair roots under magnification

8.4.6.2.4 Combination Possibilities and practical advice

The trichogram can be combined with global photographs and can be performed regardless of hair color. The cut hair shafts can be embedded longitudinally and examined for hair shaft defects or under polarizing microscopy. In addition cut hairs can be used for biochemical analyses. The trichogram should be reserved for selected cases such as loose anagen hair or when hair root analyses, as in anagen dysplastic effluvium, are decisive for the diagnosis.

8.4.7 Phototrichogram (PTG)

The PTG is a non-invasive, reproducible method with the basic principle of taking a close-up photograph of a certain defined scalp area. Before the first photograph is taken the hairs in the defined area are closecut. After certain periods repeated photographs are taken.

The PTG allows in vivo measurements of the hair growth cycle (anagen %), the total number of hairs in a certain area, hair density (n/cm²), linear hair growth rate (LHGR; mm/day), and hair thickness.

The systems used and approved nowadays are explained below.



Fig. 8.8 **a** Anagen hair; **b** telogen hair; **c**: catagen hair; **d** anagen dysplastic hair; **e** (#) Dystrophic and (*) broken hair [10]

8.4.7.1 Conventional and Contrast-Enhanced (CE) PTG

8.4.7.1.1 Introduction

With the invention of contrast-enhanced PTG, the method achieves a resolution almost equal to that of transverse microscopy of scalp biopsy samples. Through the measurement of obvious shortening of the anagen phase in the absence of hair miniaturization, the method is able to detect a subclinical phase of AGA [84].

8.4.7.1.2 History

The PTG was introduced by Saitoh in 1970 [72]. Several variants of the PTG have become popular for evaluating hair in the clinic and in clinical research trials. Phototrichogram without automated analysis was used by Blume et al [7] in 1991 for vellus hair diagnostics.

By using immersion oil (scalp immersion proxigraphy photographic method) and combination with the contrast enhancement method of Van Neste [84], CE-PTG has become a valuable instrument in hair loss diagnosis. The PTG has been compared with the unit area trichogram [71] and comparable results for anagen hairs were obtained with both methods.

8.4.7.1.3 Technology

The conventional PTG is limited by the resolution of the photograph and when there is low natural contrast between hair and skin color. Furthermore hair diameter and pigmentation are significantly decreased by the hair follicle miniaturization process of AGA. Therefore, conventional PTG, especially in AGA diagnostics, has its errors and will not be explained further here. The CE-PTG, as the improved, state-of-the-art version, has eclipsed the standard PTG and is discussed below.

8.4.7.1.3.1 Indication

The CE-PTG is a potent method for analysis of hair growth and loss.

The CE-PTG is used to detect early changes of decreased (total and growing) hair density and hair miniaturization at the single hair level, i.e., before the disorder becomes clinically noticeable, especially when diagnosing a male with AGA. This method can be applied to body hair as well [82, 85].

8.4.7.1.3.2 Technical Procedure

First of all the area of interest has to be chosen appropriately, according to the suspected diagnosis. In the case of AGA two progression areas, at the vertex and/or the receding hair line, and one control area, such as the occipital region, should be observed.

The photographs of the scalp areas are taken twice at intervals of 2–5 days, depending on the diagnosis in question or, in clinical hair growth trials, the suspected effectiveness of the substance being tested. At the first visit (day 0) all hairs in the three well-defined areas (1 cm^2) are trimmed 1 mm from the skin surface. At both visits the hair sites are covered with a transient (brown or black) hair dye for contrast enhancement, especially in patients with fair skin types. Thus blond, grey or vellus hairs are silhouetted against the light-colored skin and better visibility is achieved. Afterwards photographs with threefold enlargement are taken with a macro camera (Medical Nikkon lenses) using the scalp immersion proxigraphy method, which involves using close-up photography, where the scalp is viewed under a glass slide with a drop of immersion oil. This increases the resolution of the image and gives it more clarity under similar magnification conditions [87].

It is fundamental to ensure that exactly the same area is seen on both photos.

The individual hairs on both pictures are pairwise located and compared:

- Substantial elongation on the second photo reflects hair growth and indicates anagen
- Moderate elongation reflects catagen
- No elongation reflects resting
- A missing hair in the second picture suggests a hair shedding process.

8.4.7.1.3.3 Evaluation Parameters

- Total number of hairs in a certain area (n)
- Total hair density (n/cm^2): this includes all hairs in the defined area (1 cm^2)
- Anagen hair density: the ratio of growing hair and all visible hair per area multiplied by 100
- Linear hair growth rate (LHGR; mm/day): the change in length of the renewable hair (hair length in the second photo minus the hair length on day 0) between the times the two photos were taken
- Hair thickness: compared with a calibrated 40-µm ruler: <40 µm = thin hair; >40 µm = thick hair.

To get more reliable information the procedure is oftentimes repeated after the same interval and the pictures are compared with the baseline photograph once again.

8.4.7.1.3.4 Complications

Hair that remains inside the scalp cannot be detected. When dying is not performed correctly, superfluous remaining hair dyes in furrows mimic hair. Several investigators have attempted to automate the process of monitoring hair growth via PTG, although overlapping hairs and various artifacts have proven to be major obstacles to computerized measurement. Assessment of hair diameter is also unreliable unless magnifications in the order of ×20 are used [17].

Without a computerized analysis the method is laborious and time consuming.

8.4.7.1.3.5 Combination Possibilities and Practical Advice

In studies the CE-PTG has been combined with global photographs as an additional instrument for hair growth/loss diagnostics.

The method was applied successfully in different genetic conditions, including male pattern baldness. The technology is able to document the earliest changes in hair growth in AGA in men and is mainly used in clinical therapeutic trials.

8.4.7.2 Automated PTG: TrichoScan

8.4.7.2.1 Introduction

TrichoScan is, compared to conventional and CE-PTG, an investigator-independent, automated software program, validated by Good Clinical Practice (GCP), for the analysis of hair growth, which was developed as there was need for a sensitive tool to automatically monitor hair loss and the response to treatment. TrichoScan operates with defined values for intra- and interclass correlation between the same and different investigators. TrichoScan software analysis relies on images taken from a small analyzed area of the scalp, which is barely visible after the measurement procedure is completed.

8.4.7.2.2 Technology

8.4.7.2.2.1 Indication

TrichoScan software has been described and validated to monitor and measure hair growth in pattern alopecia [41, 42, 43, 44]. TrichoScan is not suitable for body hair or for following other hair diseases such as alopecia areata; neither is it a diagnostic tool. For the TrichoScan software analysis to be accurate, the program must be supplied with images taken from clean skin with good contrast between the hair fiber and the skin itself. Any remnants of hair dye, dark melanocytic moles, or dark scalp skin will diminish the contrast between the skin and the hairs and the analysis will not be accurate.

8.4.7.2.2.2 Technical procedure

For a TrichoScan analysis to be conducted, a transitional area of hair loss between normal hair and the balding region must be chosen and evenly clipped (Fig. 8.9).

Gray or fair hairs have only limited contrast with light scalp skin; therefore, the clipped hairs within the target area are dyed with a commercially available solution (e.g., Goldwell topchic, black 2N, Darmstadt, Germany). The approach of dyeing the hairs for hair growth studies has been described to give the same results as those with uncolored hairs. The dye product supplied with TrichoScan is best applied using a wooden spatula after having been mixed 1:1 with development cream. The dye is applied to the shaven scalp area and must remain there for 15 min. Longer dyeing periods lead to coloring of the scalp skin; shorter periods result in inadequately dyed hair. Both results are equally unsuitable for subsequent evaluation. After dyeing the hair,



Fig. 8.9 Hair clipping for TrichoScan analysis

the colored area is cleaned with an alcohol solution and, while the area is still wet, images are obtained with a digital camera such as Canon Powershot A95 fitted with a close-up microscopy attachment. All systems must be equipped with a rigid "contact lens," which ensures that the images are always taken at the same distance from the scalp.

The camera must be pressed onto the scalp, therefore the hairs are always flattened relative to the skin and camera. Images are usually taken immediately after clipping and hair dye application (Fig. 8.10) and later at different times depending on the clinical study protocol.

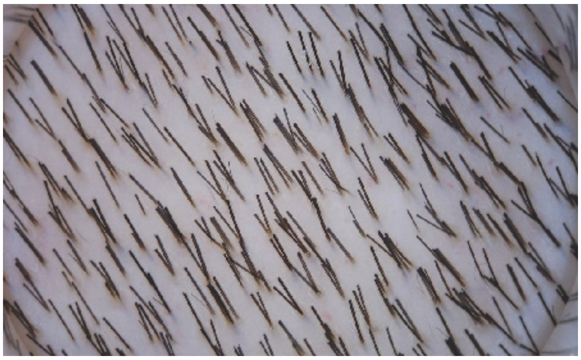


Fig. 8.10 Dyed hair 3 days after clipping photographed with the rigid contact lens of the TrichoScan

8.4.7.2.2.3 Suitable images for TrichoScan

As an automated image analysis tool, accurate TrichoScan results strongly depend on the image quality.

During clinical trials all clipped areas are landmarked with a central, single slightly red tattoo, which serves as a visible reference point throughout the study. As a digital tool, TrichoScan will always analyze the same image consistently and calculate the same results time and time again. It is also considerably quicker than manual counting and allows relatively inexperienced technicians to obtain consistent and accurate results. After taking the image the software then analyzes the scalp hair images by following a certain sequence of steps outlined below.

8.4.7.2.2.3.1 TrichoScan Parameters

- Hair density (n/cm^2): with the TrichoScan-Professional software edition it is possible to calculate the number of hairs detected (hair count) and hair density (n/cm^2). It is important to note that TrichoScan cannot pick up hairs which are too short for analysis. In addition, due to the resolution of digital cameras the TrichoScan software cannot detect very fine (approx. <6–10 µm in diameter) hairs. However, as digital camera resolution progressively improves this limitation may be resolved in the future.
- Terminal hair density (n/cm^2): by definition, a terminal hair is thicker than 40 µm. The relative number of terminal hairs is also given.
- Vellus hair density (n/cm^2): by definition a vellus hair is thinner than 40 µm. The relative number of vellus hairs is also given.
- Mean (µm) and cumulative hair thickness (mm): the research edition of the software will measure these parameters as well.
- Telogen hair count (n/cm^2): in the definition of the TrichoScan procedure, a telogen hair is a hair that has not grown in the 3 days after hair clipping in which hair stubble is left behind. In that sense, growing hairs are judged as anagen and non-growing hairs as telogen hairs.
- Anagen hair count (n/cm^2): in the definition of the TrichoScan procedure, an anagen hair is a hair that is detectable 3 days after *complete* hair clipping. Within this time only anagen hairs should grow significantly. During catagen hair growth stops and in telogen there is no longer hair growth but only some hair shaft elongation due to the so-called exogen phase of the hair cycle where the hair is eventually pushed out. In order to measure only those hairs which grow (>0.20 mm; anagen hairs) hairs must be clipped completely to the skin surface and 3 days later the clipped area needs a hair dye application and the image is made to analyze hair density. Due to the fact that the TrichoScan also measures hair length, it can easily calculate the rate of hair growth over the 3-day duration after hair clipping. Any drug, such as finasteride for the treatment of AGA, which increases the number of anagen hairs over time will result in an increased "anagen hair count" and this can be measured with the TrichoScan (Fig. 8.11).

8.4.7.2.2.4 Validation of Results

Validation studies under GCP rules (Bioskin, Hamburg, Germany) showed an overall TrichoScan reproducibility of approx 99% if one or more investigators took an im-

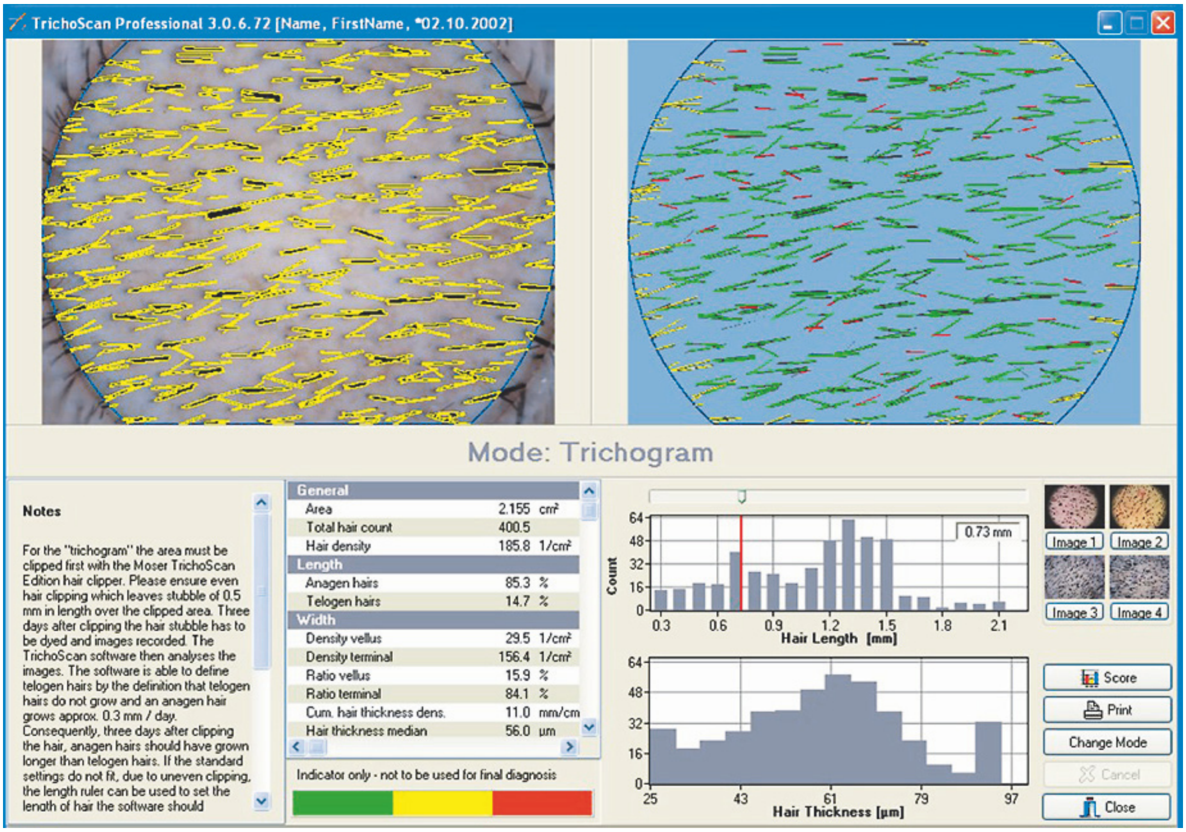


Fig. 8.11 Typical screenshot of the TrichoScan result presentation

age; no data variability was apparent if the same image was analyzed several times and there was a highly statistically significant correlation of TrichoScan to manually evaluated images of 0.967 for hair density and 0.981 for terminal hair density.

8.4.7.2.2.5 Complications

It is mandatory to clip and dye the hairs. Therefore, some patients may complain about the shaved bald spot. However, when using a suitable measurement site, this can usually be covered with neighboring hairs. Sensitization to the hair dye has to be excluded.

8.4.7.2.2.6 Combination Possibilities and Practical Advice

The TrichoScan can be combined with global photographs. The primary advantage of this technique is that it can be used for a patient's follow-up during treatment. The measurement site must not be in the parting or the whorl as it would be visible afterwards. From clinical experience, TrichoScan is a good tool to increase patient compliance.

8.4.8 Videodermoscopy

8.4.8.1 Introduction

The standard methods used to diagnose scalp and hair disorders (e.g., simple clinical inspection, pull test, biopsy) vary in sensitivity, reproducibility, and invasiveness. Studies on a few entities suggest that use of videodermoscopy can improve clinical accuracy. Use of videodermoscopy in the clinical evaluation of scalp and hair disorders improves diagnostic capability beyond simple clinical inspection and reveals novel features of disease, which may extend clinical and pathogenetic understanding [68].

8.4.8.2 Technology

8.4.8.2.1 Indication

Videodermoscopy is a non-invasive technique initially used for capillaroscopy or for in vivo evaluation of pigmented lesions, but has now proven to be a useful tool for studying in vivo scalp and hair disorders.

8.4.8.2.2 Technical Procedure

A videomicroscope equipped with various objective lenses (from ×20 through ×1000) is used. The magnification enhances the images of scalp and hair, and detects the hair shaft in the follicle (if present) and its length, diameter, and possible anomalies. All digital images may be stored for further controls.

8.4.8.2.3 Complications

There are no technical difficulties but the examiner has to be trained to judge the scalp observation correctly. The use of immersion oil is recommended for high magnification.

8.4.8.2.4 Combination Possibilities and Practical Advice

Videodermoscopy is useful for the differential diagnosis between cicatricial and non-cicatricial alopecia, and between alopecia areata and trichotillomania. Follicular atrophy (Fig. 8.12) or keratotic plugs (Fig. 8.13) can easily be identified in the follicular openings. In alopecia areata (Fig. 8.14) and AGA (Fig. 8.15) peripilar dots may be present. In trichotillomania, hairs broken at different distances from the scalp can be observed. In addition, one may study the vascular pattern of the scalp, using the epiluminescent mode [19, 48, 68].

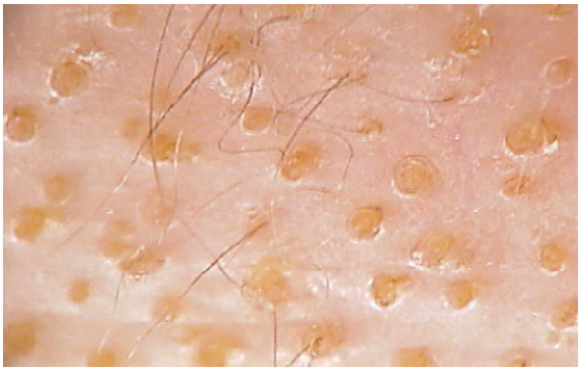


Fig. 8.13 Keratotic plugs are present in the follicle openings of chronic alopecia areata



Fig. 8.14 Peripilar signs in alopecia areata. Note the cadaverized hairs (#) and exclamation point hairs (*)



Fig. 8.12 Absence of follicle openings in lichen planopilaris

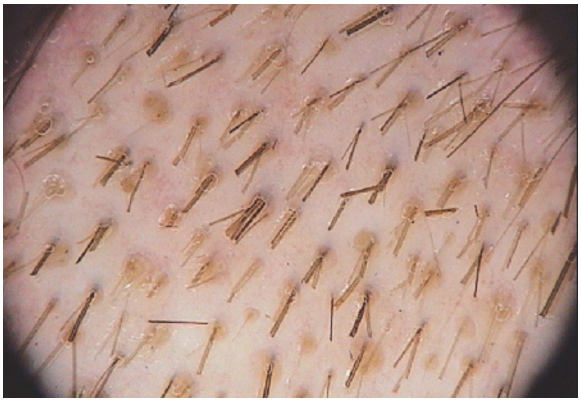


Fig. 8.15 Peripilar signs reflecting the presence of perifollicular infiltrate in androgenetic alopecia

8.5 Structural and Functional Investigation

8.5.1 Mechanical Test of Hair Quality (Elasticity, Strength, Fragility)

8.5.1.1 Introduction

Physical properties of hair directly result from the organization of the various structural elements of the fiber (proteins, fibrils or cells) which are responsible for the hair's condition and appearance. The physical properties are investigated using tools that evaluate the integrity of the internal structure of the fiber, its alterations in response to cosmetics or the environment, and the effect of treatments applied.

8.5.1.2 Mechanical Properties

Measurement of mechanical properties is the simplest means of apprising the integrity and attributes of the hair fiber. A slight modification in chemical composition or structure of hair may greatly alter its mechanical properties.

Tensile properties of hair are classically measured by an extensometer, which measures the stress/strain curve of single hair fibers. Four types of stress can be applied to solid structures: extension, compression, flexion, and torsion. In this way the behavior of the material under strain of varying amplitude and breakage can be investigated.

8.5.1.3 Technique

The tensile properties are measured with a tensile tester (e.g., Diastron, UK), an aperture in which the hair is fixed between two ferrules in a sample cassette of the instrument. A constant speed of extension is exerted on the hair fiber until it breaks.

Indication:

- Evaluation of treatment effects on hair
- Cosmetic product testing or pathological condition of the hair

See Table 8.4 for obtainable measure values.

8.5.2 Optical Light and Polarizing Microscopy

8.5.2.1 Introduction

Light microscopy, bright field optical microscopy, and polarized light microscopy are the fastest and simplest methods of optical microscopy in daily practice.

8.5.2.2 History

Many scientists are accredited as being the innovator of the first compound microscope, for example Hans Janssen in 1590, Galileo Galilei in 1603 and Christiaan Huygens in the late 1600s.

8.5.2.3 Technology

8.5.2.3.1 Indication

Hair shaft anomalies and unknown increased fragility of hairs.

8.5.2.3.2 Technical Procedure

To examine hair structure, approximately 10–20 hairs are clipped close to the scalp surface and placed directly onto double-sided tape (15 mm wide) attached to a 25-mm microscope slide. The collected hairs are realigned, thereby allowing easy visualization within the microscope. Another technique is to use medium (Eukitt), which enables storage of the hair for later evaluation and teaching. Depending on the clinical diagnosis, examination of the complete hair length may be necessary. Thus hairs are embedded from the proximal to the distal end in sections on different glass slides. This may be useful, e.g., to distinguish between the distal and proximal types of trichorrhexis nodosa.

By light microscopy direct evaluation of the hair shaft, its anomalies, thickness, form or twists is possible (Fig. 8.16, 8.17).

The same embedded hair specimen can be analyzed by polarizing microscopy too.

For polarizing microscopy a polarization filter (Nikolprisma) generates the polarized light. The physical principle is a change of refraction from one side to another of the hair shaft along its longitudinal course. Polarizing microscopy helps the detection of disorders of protein composition and keratinization or storage, e.g., in trichothiodystrophy with the tiger tail pattern or in monilethrix (see Chap 14).

Table 8.4 Measurement parameters of tensile properties of a hair fiber

Parameter	Calculation and results
Young's modulus of elasticity (E, Y)	Young's modulus of elasticity (*E*), measured in Pascal (Pa=N/m2), is a physical material constant which specifies the stiffness of a material under constant ambient conditions such as temperature and humidity. It describes the maximum point of the stress slope until its plateau (Hookean region). The higher the stiffness, the greater *E*. $E = \sigma/\varepsilon = \Delta F*L/\Delta L*A$ [Pa] σ: tensile stress; ε: tensile strain; ΔF: change in force induced by a change in length (N); ΔL: linear change of the fibers' length; *L*: equilibrium length of the fiber; *A*: cross-sectional area (m^2) Wet hair: $E = (1.5–2.0) \times 10^9$ Pa Dry hair: $E = (3.5–4.5) \times 10^9$ Pa Complications: When reporting E, the pre-gauge must be specified.
Yield stress	The stress at the maximum point of the stress slope until its plateau (Hookean region). Aprox. Size: $(69.7–93.3)\times10^6$ Pa
Breaking strength	The maximum of the stress-strain-curve when the hair breaks. $(254\pm33.7) \times10^6$ Pa For measuring only the breaking strength a simpler test arrangement can be chosen. The device developed by Wickett [93] is based on a lever principle. A meter stick pivots on a bolt through a hole in the center. The hair is fastened to one end and a weight on a sliding hanger is moved slowly and carefully along the other side, away from the center hole. Breaking strength: $Wt*(L_2/L_1)–W_c$ W_t: Total weight of the sliding hanger and attached weight; L_1: Distance from the center hole to the hair; L_2: Distance from the center hole to the slide at break; W_c: Weight of the clip used to hold the hair.

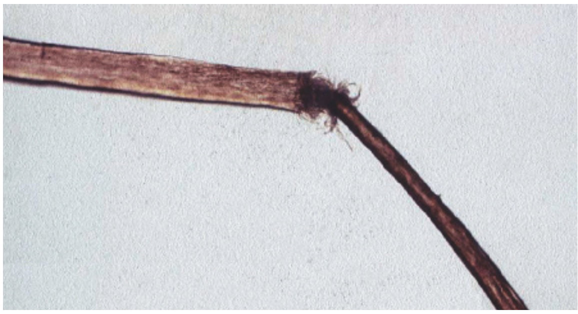


Fig. 8.16 Trichorrhexis nodosa in light microscopy

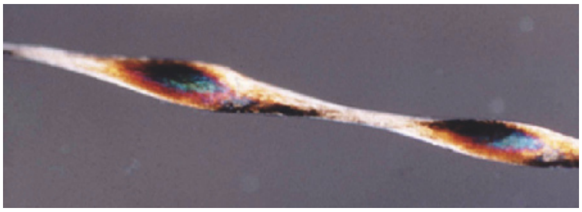


Fig. 8.17 Typical node and internode section of hair in monilethrix examined in polarizing light

8.5.2.3.3 *Complications*

Errors in embedding with hairs overlaying one another may render a correct examination difficult.

8.5.2.3.4 *Combination Possibilities and Practical Advice*

Light and polarizing microscopy can be combined with any other trichologic diagnostic technique. In genetic disorders with protein defects it is useful to store hair for subsequent biochemical analysis.

8.5.3 Confocal Laser Scanning Microscopy (CLSM)

8.5.3.1 Introduction

Confocal microscopy, also known as laser scanning microscopy, provides high-resolution images.

The method was developed by Marvin Minsky in 1953, patented in 1957, and the first picture of a biologic

sample (an unstained brain and ganglion cells) was published in 1967 by Egger. Despite this early demonstration CLSM was not widely applied until the recent advancement of digital image storage and processing [80].

An object is rastered via point-by-point exploration with a laser beam, which is at most zoomed in at a focus level to the investigated probe.

The procedure can be advantageously adapted to studies of cylindrical objects such as human hair.

It requires minimal sampling preparation, and the hair can be observed in its natural environment with less damage caused than by other microscopic methods such as scanning electron microscopy [35].

8.5.3.2 Technology

8.5.3.2.1 Indication

Confocal laser scanning microscopy generates non-invasively a three-dimensional (3D) image of the hair's surface and different internal structures. It produces serial optical sections of thick specimens and reconstructs 3D images by using a spatial pinhole to eliminate out-of-focus points, detecting only the light within the focal plane. The image quality thus obtained is much better than that of conventional wide-field view. It provides fluorescent images either by exploiting the natural fluorescence of keratin or by adding different fluorescent dyes such as markers of different structures. The technique analyzes the surface (size of the scales, optical properties of the hair such as opacity or brilliancy), internal structures of the hair (cortex and medulla fibers), and the emission spectrum. It is a useful non-destructive method for objects with curved surfaces and does not require any sample preparation.

8.5.3.2.2 Technical Procedure

Technically, the CLSM combines light microscopy, confocal imaging, video and scanning microscopy, and coherent or laser-illuminated optics [27].

The stimulating light is focused by a lens into the hair sample, which is simply attached to a microscope slide.

The reflected light is focused through a lens with the same focal point (confocal) on the detector, mostly a photomultiplier. The pinhole, usually 10–20 pm, cuts away the light that comes from the out-of-focus planes of the specimen. Thus, only light coming from the in-focus plane (continuous lines) passes through the pinhole and is detected. The whole mechanism functions under computer control and operates by the scanning of the focused beam in a raster or meandering fashion through a specimen [80].

The confocal scanner has a two-channel configuration that permits simultaneous imaging of reflected light (Fig. 8.18) and fluorescence contrast (Fig. 8.19).

The graphical representation of the outer cuticle, the border of cuticle cells, the medulla, nuclear remnants of the cortical cells, the differentiation of medulla and cortex as well as transversal optical sections and the 3D reconstruction of cuticle envelope and medulla channel are obtained [35].

8.5.3.2.3 Complications

Confocal laser scanning microscopy is not suitable for daily routine use but is useful in clinical and cosmetic research. The technique needs a highly trained operator to obtain exploitable pictures needed for correct interpretation.

8.5.3.2.4 Combination Possibilities and Practical Advice

Confocal laser scanning microscopy is a rapid, easy, non-destructive method for studying the localization of fluorescent stains of the internal structure or for observing the surface of the cuticle. It is useful for obtaining "dynamic studies," such as the routes of penetration of fluorochromes into the cortex, and "optical sections" of the specimen [35].

The condition of the hair surface can be evaluated according to the chemical or physical injuries sustained. Surface deposits can be observed in terms of thickness, homogeneity, and brilliancy as well as their resistance to cosmetic treatments.

The routes of penetration of fluorochromes into the hair structures can be investigated dynamically [35].

8.5.4 Electron Microscopy

8.5.4.1 Introduction

Both SEM and transmission electron microscopy (TEM) are used in high-resolution trichological s, despite their difficult sample preparation methods.

The first electron microscope prototype was built by Ernst Ruska and Hans Knoll in the early 1930s. General use of SEM became available in 1965; TEM was designed in 1940 by Von Borries and has been developed further.

The SEM is a valuable instrument for obtaining detailed architecture of the human hair surface; TEM needs very thin samples and more extensive preparation for analysis, but the rewards are images of structures at the atomic level [18].

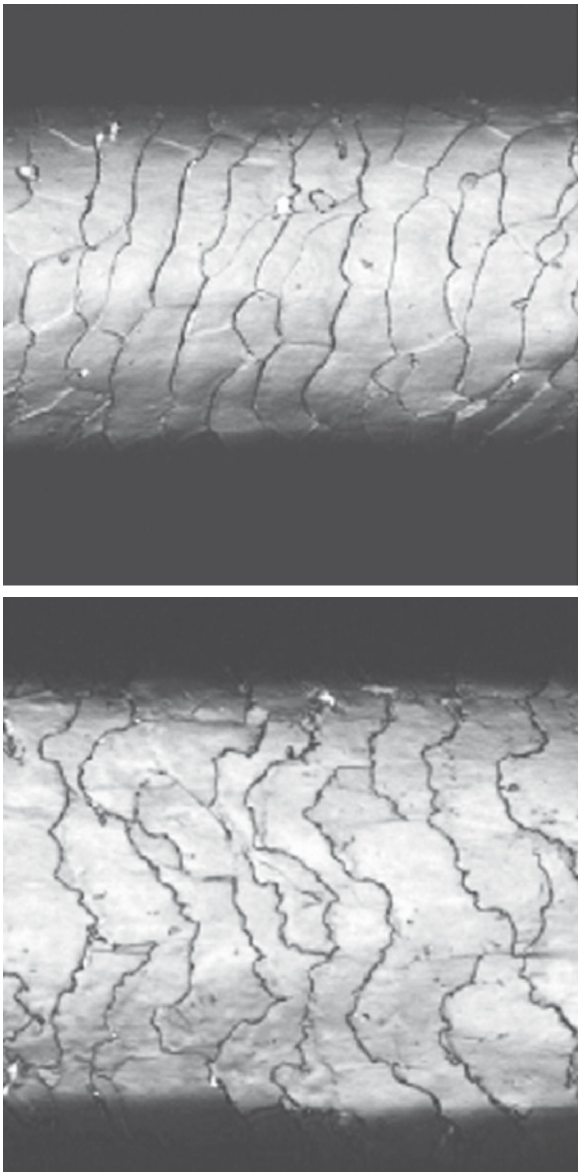


Fig. 8.18 Reflection images of the hair cuticle. On the *upper* scales with regular edges of a normal hair, on the *lower* scales with damaged indented edges of a weathered hair

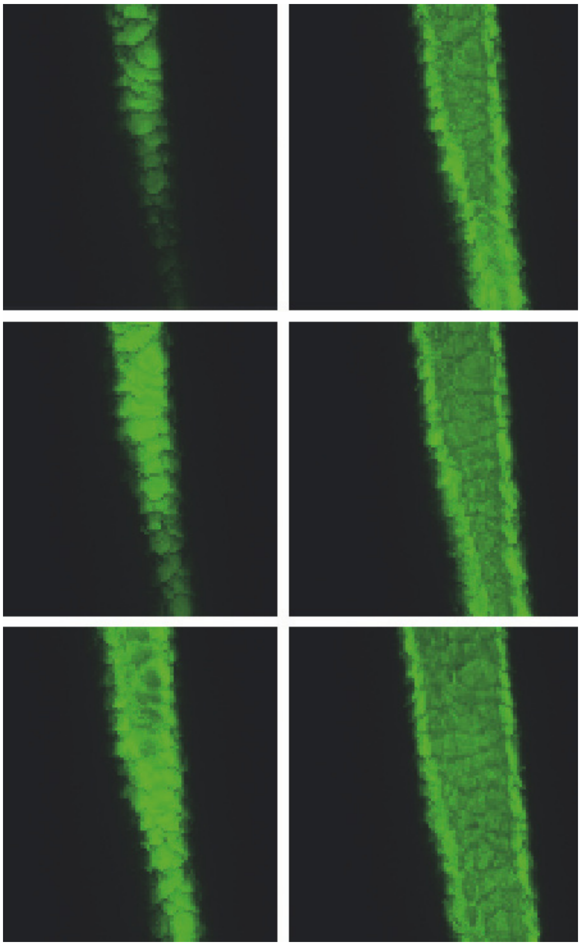


Fig. 8.19 Optical sectioning of hair from the surface throughout the inside of the cortex, from upper left to lower right

8.5.4.2 Technology

8.5.4.2.1 Indication

It is used when high-resolution images of the hair cuticle surface with illustrations of hair shaft abnormalities and longitudinal or transversal images of the inner structures are required.

8.5.4.2.2 Technical Procedure

Electron microscopy, compared to optical microscopy, is distinguished by its high spatial resolution in the nanometer range, achieved because electrons have a short De Broglie wavelength (Fig. 8.20a,c).

8.5.4.2.3 Complications

The pretreatment of the hair required for electron microscopy compared to atomic force (AFM), confocal or optical microscopy is much more extensive and can lead to artifacts. A further problem is specimen damage caused through the excessive heat of the electron beam. Electron microscopy has high acquisition and maintenance costs.

8.5.4.2.4 Combination Possibilities and Practical Advice

Both TEM and SEM can be combined with other microscopical techniques such as light microscopy and CLSM to obtain an overview of the hair sample; the examiner can keep the number of samples for SEM or TEM low, which saves both time and costs.

8.5.5 Atomic Force Microscopy (AFM)

8.5.5.1 Introduction

The atomic force microscope is a combination of the principles of the scanning tunneling microscope and the stylus profilometer.

The technique of AFM was invented by Binnig, Quate, and Gerber [5] as a device to measure any type of force; not only interatomic forces, but also electromagnetic forces. For hair O'Connor et al. used the method as a quantitative real-time method to analyze human hair morphologic changes under ambient conditions [55].

8.5.5.2 Indication

Atomic force microscopy supplies 3D images (profilometry) with high resolution at the nanometer scale, and qualitative and quantitative measurements of the sample, giving a mathematical description of the surface (Fig. 8.21).

It operates without any sample preparation, avoiding contact between the tip probe and the sample surface. It can be useful to investigate the roughness and the weathering of the cuticle, and to measure lifting of the scales. This technology provides complementary information on hair shaft condition.

8.5.5.3 Technical Procedure

The hair is placed on a microscope slide coated with double-sided adhesive tape and analyzed. The hair is then placed on an x-y-z piezo-translator and scanned with a tip probe mounted on a cantilever (flexible arm). The deflections of the cantilever, due to the interaction forces between the sample surface and the tip, are detected by a laser beam reflected from the back of the cantilever to a photodiode, and processed by a computer, providing a topographic image at molecular or atomic resolution (more than 1000 times better than the optical diffraction limit).

8.5.5.4 Complications

Atomic force microscopy is not for clinical practice, but in hair cosmetology it can assess the effect of dyeing, bleaching, perm, or conditioners. The operator needs a good training to comprehend the data and interpret the results. However, AFM is limited to measurement of the topographic morphology perpendicular to the sample plane, meaning that re-entrant surfaces (i.e., spaces obscured by the main surface) and subsurface information cannot be detected, in contrast to SEM or confocal microscopy using fluorescence [34].

8.5.5.5 Combination Possibilities and Practical Advice

General features of the hair shaft (distal free edges, surface and distribution of the scales) are observed and the lifting and size of the scales may be measured [79].

The AFM can be used not only as an imaging technique, but also as a tool for quantitative assessment of the effects of human hair treatment [94]. The advantages of this non-invasive method are that it requires

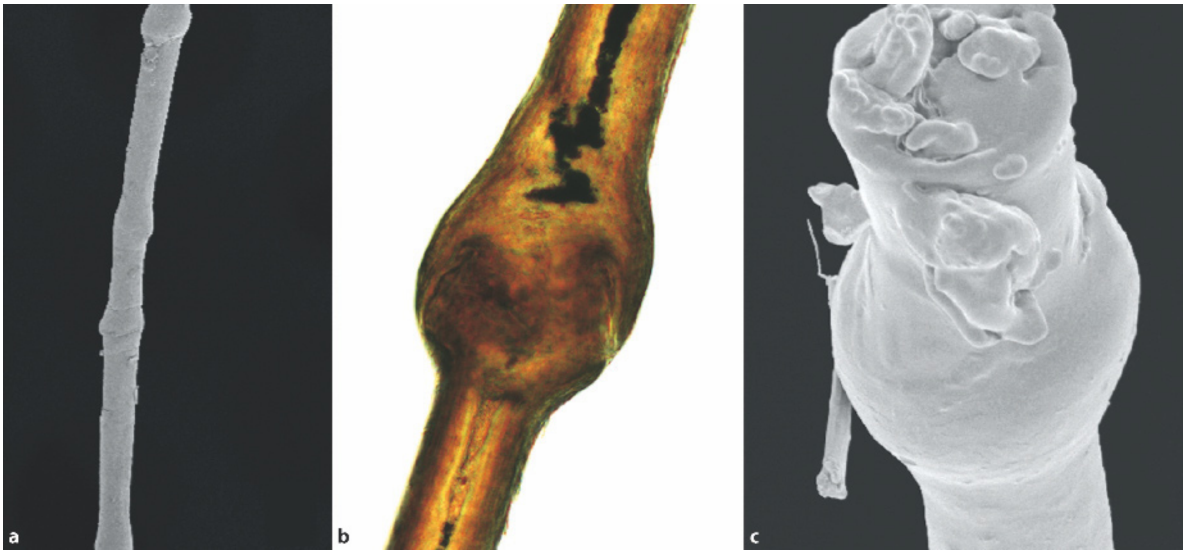


Fig. 8.20a–c Multiple typical features of Trichorrhexis invaginata along the hair shaft (**a**), close up view of one tulip-like invagination with the lower ball and upper cup portion in (**b**) light microscopy and (**c**) SEM

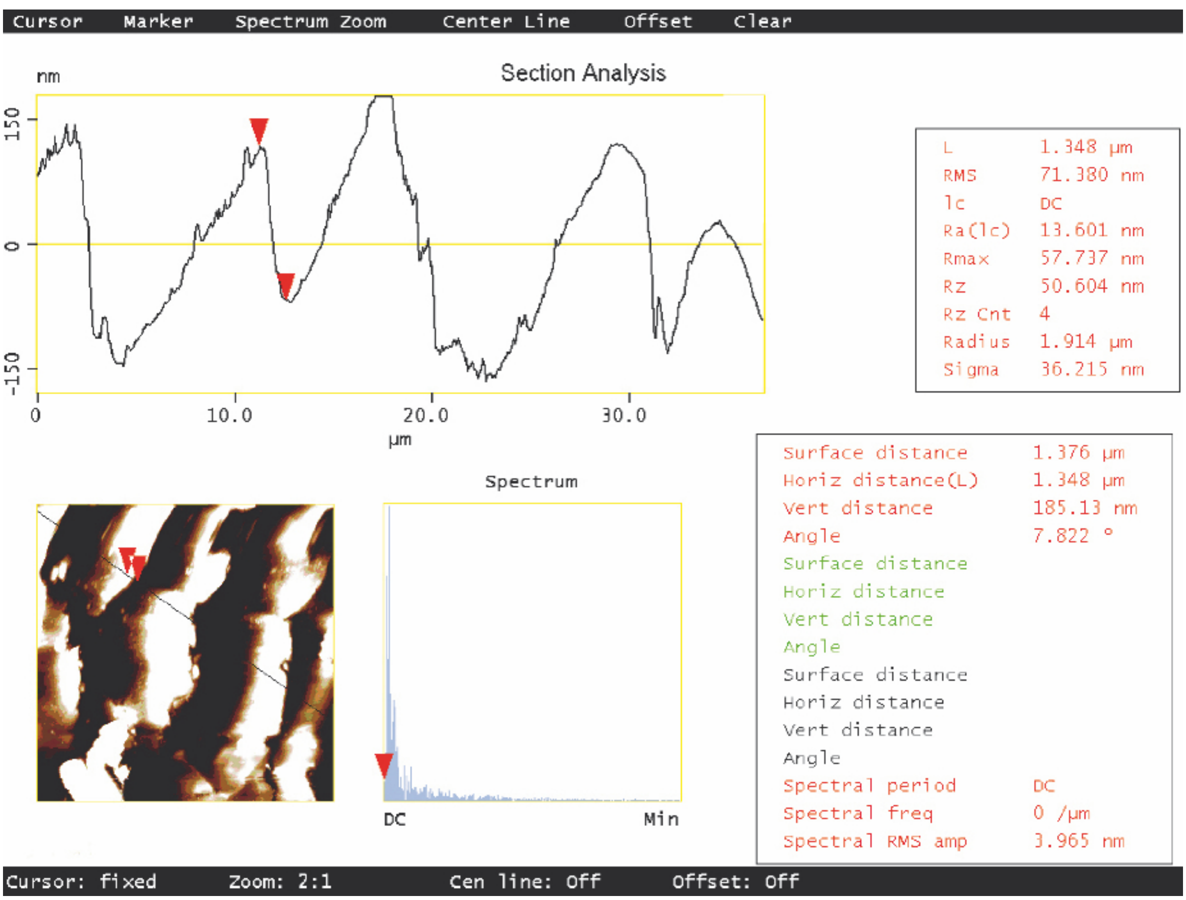


Fig. 8.21 AFM image of a Caucasian hair treated with an alkaline solution. Surface profile of cuticle scales of hair at the level of the black transverse line. Measures in the tables are taken at the level of the red arrows

no special and extensive sample preparation like single electron microscopy, and yet it provides accurate topographic information about the fine sample hair's outer surface structure, enabling height differences of less than 1 nm to be measured [34].

8.5.6 Optical Coherence Tomography

8.5.6.1 Introduction

Optical coherence tomography (OCT) is able to provide highly reproducible in vivo and ex vivo measurements of hair shaft thickness, including the inner-hair variation of diameter and shape.

The application of OCT was developed by Huang in 1991 [45] for research on human retina. In 1995 Schmitt introduced the method to dermatology and recently OCT was established as a diagnostic tool in trichology [9].

8.5.6.2 Technology

8.5.6.2.1 Indication

Optical coherence tomography can be used for trichological examination, especially for measuring hair diameter, cross-section surface, and hair shape. In the future it may help to investigate the influence of hair growth promoting agents in clinical studies (Fig. 8.22).

8.5.6.2.2 Technical Procedure

Optical coherence tomography uses low-coherence interferometry (Michelson type) to produce a two-dimensional image of optical scattering from internal tissue microstructures in a way that is analogous to the ultrasonic pulse-echo image which works with ultrasound [45].

In this procedure the running time of the near-infrared signal to a specimen and back is compared to a known reference signal (Fig. 8.23).

Lateral scanning of the axial OCT scans results in two-dimensional cross-sectional images; three-dimensional images are also possible [89].

8.5.6.2.3 Combination Possibilities and Practical Advice

In trichological diagnosis OCT is used to determine hair shaft diameter, cross-sectional surface area, and hair shape, similar to histology but in vivo. Optical microscopy and CSLM have the potential to define the transverse caliber of hair, but these methods have the disadvantage that they display the diameter in only one plane and hair is frequently not symmetrical, limiting their usefulness.

The OCT pictures the cross-sectional surface as well as the longitudinal and transversal diameters; it can be used in clinical studies to follow in vivo hair shaft changes over time.



Fig. 8.22 Use of a fiber-linked OCT system for hair shaft examination in order to measure in vivo hair shaft diameter

8.5.7 Hair Analysis Methods

8.5.7.1 Introduction

There are two main methods of spectrographic analysis of hair elements: destructive, which requires a significant "mass" or volume of samples (50–200 mg of material), and non-destructive, which provides data on a single hair (a few millimeters of hair is enough).

The analysis of the bulb and the hair shaft is reserved for research purposes and is still a long way from being available for routine investigations.

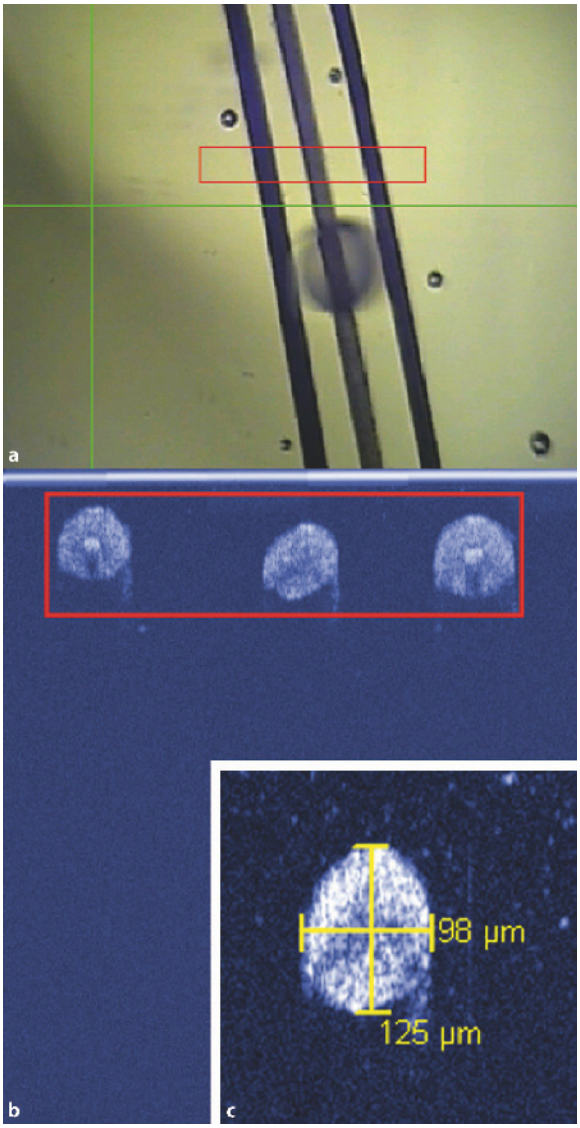


Fig. 8.23a–c Photographs of the hair shafts observed by OCT. **a** The red-framed cut-out represents the area scanned by the OCT seen in **b**,**c** Horizontal and vertical diameter of a hair measured by OCT

The first serious hair analysis using physical techniques such as neutron activation analysis (NAA) or energy dispersive X-ray analysis (EDX) was presented in 1973. Based on the analysis of hair in relation to the environment, especially exposure to mercury compounds, it was shown that hair stores heavy metals in the growing hair shaft. Later, variations of different metals in hair were presented in patients with various mental state alterations compared to those found in control patients.

8.5.7.2 Technology

8.5.7.2.1 Indication

Hair analysis methods are indicated for evaluations of genetic disorders, to check the relationship between the amount of an element in the hair and the patient's health status (physico-chemicals properties of hair in disease, i.e., in Menke's disease: dysfunction of copper absorption). They are indicated in forensic and environmental sciences (analysis of hair fiber may give information on the time sequence of exposure to and intake of certain substances). The results from other body specimens can only be used as a measure of recent exposure or of the amount removed from the body; hair, in contrast, can provide a historical exposure record [21].

8.5.7.2.2 Technical Procedure

Hair samples are obtained by plucking hairs with the same technique as the trichogram. Since the scalp hair is continuously exposed to the environment, external contamination should always be considered. Hence the non-exposed part of a growing anagen hair fiber should be the specimen of choice. Usually, the sample is taken in the temporal area with respect to the goal of the investigation. (The temporal region is excluded from male pattern alopecia type of hair loss and represents an area with normal anagen/telogen hair follicle distribution in both sexes.)

8.5.7.2.3 Combinations and Practical Advice

The validity of hair analysis depends more on the mode of sample collection and preparation of the hair for analysis, than on the specific sensitivity of the techniques. Contamination is one of the most serious problems encountered in element analysis of hair fibers. It should be remembered that, due to the effect of the detergents found in shampoos, the hairs may have lost some of their lipids and protein components, and also that the shampoos may have added some strange elements such as sulfur, chlorine, potassium, calcium, iron, and zinc. The significant differences in the elements Fe, Zn, and Se in the hair before and after washing are observed in Table 8.5. The part of the hair used for analysis should be sampled close to the infundibulum of the hair follicle (it is the least contaminated part).

An overview on destructive methods is seen in Table 8.6.

Table 8.5 Element content before and after hair wash

Element	Amount in unwashed hair (ppm dry hair)	Amount in washed hair (ppm dry hair)
Fe	37.2±3.1	39.3±3.2
Zn	52.5±10	54.2±10
Se	1.67±0.2	1.72±0.15

Table 8.6 Overview on destructive methods for analyzing components of the hair shaft and the biochemical composition of the hair

Atomic absorption spectroscopy (AAS) Graphite furnace AAS (GF-AAS) Combustion AAS (Comb-AAS)	A method for the detection of metal levels in hair in investigation of heavy metal exposure as well as for measuring trace metal deficiency The AAS in general is an extensive method especially with regard to sample preparation and duration. The comb-AAS is described elsewhere [21]
Atomic emission spectrometry (AES) Inductively coupled plasma (ICP)	A method for detecting metal levels in hair in investigation of heavy metal exposure as well as for measuring trace metal deficiency
Gas chromatography–mass spectrometry (GC-MS) Includes enhanced methods: electron impact ionization (EI) selected ion monitoring mode (SIM) positive or negative chemical ionization (PCI, NCI)	Most frequently used method for a large variety of drugs or metabolites in hair analysis due to high accuracy at very low concentrations. Furthermore, a large number of substances can be measured in the same run with a limit of detection (LOD) of about 0.03 ng/mg for most drugs. The differences in sample preparation limit its application to a generalized approach for a larger number of drugs [62]. The GC-MS is the confirmatory test for positive results in RIA or ELISA Detectable substances: most drugs and their metabolites including ethylglucuronide and fatty acid ethyl ester, which are measurable in the same way as pharmaceuticals such as neuroleptics, benzodiazepine and anabolic steroids [22, 31, 46, 47]: Amphetamine, methamphetamine, MDA, MDMA, MDEA, ephedrine, cathine, propanloamine, PCP, cocaine, cocaethylene, codeine, dihydrocodeine, acetylcodeine, heroin, methadone, EDDP (methadone metabolite), morphine, 6-monoacetylmorphine, tetrahydrocannabinol (THC), benzoylecgonine, ecgonine methylester, anhydroecgonine methylester [22, 31]
Liquid chromatography – mass spectrometry (LC-MS)	A big advantage of LC-MS versus GC-MS is the lack of complications such as volatility, stability and issues with derivatization A further benefit is a low LOD of 1 pg/mg with the possibility of measuring single drug doses in hair as well as the measurement of more than 100 drugs in a single chromatographic run Because of its lower chromatographic resolution it must be combined with associated methods Despite its big advantages, the method remains limited to a small number of forensic toxicological laboratories because of cost [62] Detectable substances: Most drugs and their metabolites (including ethylglucuronide), as well as pharmaceuticals such as neuroleptics, benzodiazepine and sildenafil
HPLC	Drugs

Table 8.6 (*continued*) Overview on destructive methods for analyzing components of the hair shaft and the biochemical composition of the hair

Capillary electrophoresis (CE)	CE based on the separation of charged analytes through a small capillary under the influence of an electric field. CE can be applied in different modes of separation and can be combined with several detection methods Detectable substances: Many drugs and their metabolites, e.g., amphetamine, cocaine, ephedrine, MDA, MDEA, MDMA, methadone and metabolite, methamphetamine and morphine [11]
Enzyme-linked immunosorbent assay (ELISA)	ELISA is used as a screening method for drug analyses. However, positive results from immunoassays must be confirmed by a chromatographic method or any other independent technique providing equivalent selectivity. In addition, negative drug testing results should be controlled if they are detrimental to the accused in forensic science [22, 62]
Radioimmunoassay (RIA)	The first hair analyses for drugs were performed by RIA in 1979. The method is rarely used in drug analyses; the more frequently utilized immunochemical method is the ELISA As for ELISA the test has to be confirmed by a chromatographic method [22, 62]

8.5.8 Scalp Biopsy

8.5.8.1 Introduction

The scalp biopsy, mostly performed with a 4-mm cylindrical punch, is an important tool in the diagnosis of cicatricial and non-cicatricial alopecia. It is difficult but most important to select the biopsy site appropriately.

As it is an invasive technique, the indication for a scalp biopsy should be provided carefully but when necessary the intervention should not be delayed.

8.5.8.2 Technology

8.5.8.2.1 Indication

- Atrophic as well as cicatricial alopecia.
- Nonspecific inflammatory scalp diseases
- Scalp tumors
- Non-specific differential diagnosis of non-cicatricial alopecia
- Proof of hair growth
- In clinical studies.

8.5.8.2.2 Technical Procedure

8.5.8.2.2.1 Biopsy Location

It is critical to choose the biopsy site correctly. In non-scarring alopecias (e.g., trichotillomania, alopecia areata) a punch in the center of the lesion would be suitable. This is inappropriate in scarring alopecias, where instead a sample from the active peripheral margin would be suitable.

8.5.8.2.2.2 Biopsy Procedure

After selecting the site(s) they are anesthetized using 1–3 ml of a 1% lidocaine with epinephrine (1:100,000) mixture buffered with sodium bicarbonate. The local anesthetics should be injected deep in the dermis and in the superficial fat. After disinfection and assuring oneself that pain in the area cannot be felt (usually 5 min after local anesthesia; but perhaps there is better vasoconstriction after 10 min), the biopsy can be performed. The 4-mm cylindrical punch is inserted into the scalp parallel to the direction of hair growth, with rotary cutting motion through the dermis down into the fat in such a way that entire bulbs of engrained terminal hairs can be extracted and the hairs are pointing straight upward at 90°.

Afterwards the biopsy sites can be sutured with a 3-0 non-absorbable fiber.

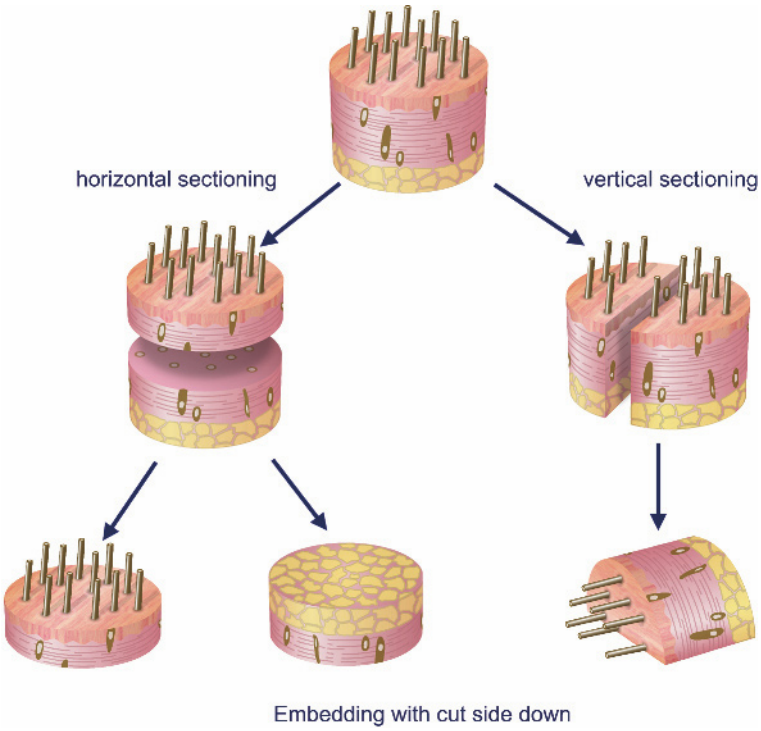


Fig. 8.24 Two scalp punch biopsy samples are used for histological investigation. One specimen is cut horizontally approx. 1 mm above the dermosubcutaneous junction. The other one is sliced vertically in equal parts. One vertical and both horizontal pieces are embedded in paraffin with cut-side down for histological diagnosis. The remaining vertical half can be stored or used for direct immunofluorescence (DIF)

Usually, two specimens are collected from the involved area: one for horizontal sectioning and one for routine vertical sectioning. If a specimen is needed for direct immunofluorescence study, the "vertical plug" is bisected before formalin fixation and one hemisection prepared for direct immunofluorescence in appropriate fixative; if possible, an additional specimen is collected from a clinically uninvolved site (usually the occiput) and processed for horizontal sections to allow comparison with affected areas [29] (Fig. 8.24).

8.5.8.2.2.3 Complications

As with all surgical procedures, scalp biopsy may be complicated by wound infection, vascular and nerve trauma.

8.5.8.3 Horizontal sectioning

8.5.8.3.1 Introduction

The horizontal sectioning method was phased in by Headington in 1984 [40] and nowadays it is impossible to imagine dermatohistology without it. There are a few different ways of specimen cutting and embedding.

8.5.8.3.2 Technology

8.5.8.3.2.1 Indication

Horizontal sectioning permit to count follicular structures: hair bulbs terminal anagen, catagen, telogen hairs, telogen germinal units, „vellus hairs", follicular units and follicular stelae (streamers).

8.5.8.3.2.2 Technical Procedure

For the biopsy procedure, see Sect. 8.5.8.2.2.2 and Fig. 8.24.

The original method of Headington states that the biopsy specimen should be carefully tightened with forceps, by no means squashed, and cut horizontally approx. 1 mm below the epidermal surface with sharp scissors or a razor blade. Both cut samples are embedded cut side down into a cassette for paraffin embedding. While slicing the paraffin block the sections become gradually more superficial in the "epidermal portion" and deeper in the "fat portion."

With the method of Frishberg the specimen is cut horizontally into three to five slices, depending on the length of the plug. Ink is applied to the deep surface of each section. Furthermore the deepest portion receives

a small dot at its apex, for better identification. The sections are laid ink-side down in a standard processing cassette for coating with paraffin. When slicing the paraffin block the sections will become progressively more superficial in all pieces. Afterwards stain with hematoxylin and eosin (HE).

For the method of Elston one specimen is bisected vertically: half for HE staining, half for direct immunofluorescence, and the second specimen is bisected horizontally in the same manner as in the Headington method and submitted for HE staining. The improvement of the method is that the three pieces of tissue for HE staining are embedded in a single cassette and later on the slide both horizontal and vertical sections can be evaluated [24].

8.5.8.3.2.3 Complications

The horizontal section of Headington can lead to confusion by slicing superficially on one hemisection and deeper on the other.

8.5.8.3.2.4 Combination Possibilities

Embedding both vertical and horizontal sections in one paraffin block, like the method of Elston.

8.5.8.4 Vertical Sectioning

8.5.8.4.1 Introduction

Vertical sectioning is the traditional method used in hair follicle histology to display whole hair follicles.

8.5.8.4.2 Technology

8.5.8.4.2.1 Indication

See Sect. 8.5.8.2.1.

Vertical sectioning provides an histological overview of the skin biopsy which provides the examiner with different informations ranging e.g. from lenght of hair follicles, size of sebaceous glands, distribution pattern of the inflammatory infiltrate around vessels, hair follicles (Table 8.7).

8.5.8.4.2.2 Technical Procedure

The whole specimen can be laterally embedded and sliced, but usually the sample is carefully vertically bisected. Half is submitted for direct immunofluorescence (DIF), and half is placed in formalin for histological study. The specimen has to be embedded cut-side down in the cassette.

8.5.8.4.2.3 Complications

In some sections are no hair follicles, so the paraffin block has to be sliced further.

8.5.8.4.2.4 Combination Possibilities and Practical Advice

Embedding both vertical and horizontal sections in one paraffin block, like the method of Elston.

One half of the vertical section is applied for immunofluorescence (IF) histology, preferably a frozen section

Table 8.7 Advantages and disadvantages of horizontal and vertical sectioning [24]

	Horizontal (transverse) sectioning	Vertical sectioning
Advantages	• Examination of all follicles in the punch biopsy (20–30) at various levels (quantify abnormalities) • Evaluation of follicle density • Determination of the total number of follicles and the stage of their growth cycle and follicular dynamics • Possible infiltrates are better seen	• The hair shaft can be evaluated along its entire length • Clear demonstration of changes at the dermoepidermal junction, papillary dermis, and subcutaneous tissue • Infiltrates can be adequately assessed by pattern recognition
Disadvantages	• Does not show changes at the dermoepidermal junction, within the papillary dermis, and within the subcutaneous fat (to avoid: laborious step sections needed)	• Fewer hairs (4–6) can be assessed per slide (to avoid: laborious step sections needed) • In some sections are no follicles

without formalin fixation. Immunofluorescence sections are mostly made for the investigation and diagnosis of cicatricial alopecia and for diseases whose antigen status is known, as well as in studies of structural identification [81]. Both direct and indirect IF histology are applied.

A vertical section and a horizontal section should both be accomplished (Table 8.7). The horizontal sectioning as well as the evaluation should be carried out by a highly qualified histopathologist.

The IF should not be used as a routine method for all scalp biopsy samples but in special circumstances and cases where the histopathology is cases (Table 8.8).

Due to its low sensitivity, IF is of limited help in diagnosing lichen planus and it does not help to differentiate pseudopelade Brocq from lichen planus. Its high sensitivity and specificity mean that IF can be of value in the diagnosis of LE.

Summary for the Clinician

Tools to diagnose and monitor hair loss, hair growth and the response to treatment must be chosen dependent whether needed for practising dermatologist, for research purpose or for clinical studies. The techniques can be classified as either invasive (e.g. biopsies in scarring alopecia), semi-invasive (trichogram, unit area trichogram) or non-invasive (e.g. global hair counts, phototrichogram, electron microscopy, laser scanning microscopy) methods. Quantitative methods for the analysis of human hair growth and hair loss are necessary to determine the efficacy of hair promoting drugs.

For *practising dermatologists* body and scalp hair distribution evaluation by different grading systems, hair pull test, dermatoscopy and computer assisted phototrichogram, and in selected cases trichogram and biopsies are helpful tools.

For *research purposes* optical coherent tomography, electron microscopy, biochemical methods, atomic force microscopy and confocal laser scanning microscopy can be used.

For *clinical studies* global photographs (global expert panel), hair weighing, phototrichogramm and different clinical scoring systems have been proven to be objective tools for documentation and evaluation of hair growth.

Table 8.8 Diseases diagnosable with histopathology and immunofluorescence (IF)

Lupus erythematosus
Pseudopelade Brocq
Postmenopausal frontal fibrosing alopecia
Circumscribed scleroderma
Cutaneous lymphoma
Traumatic alopecia
Follicular degeneration syndrome
Acne keloidalis nuchae
Alopecia parvimaculata
Stem cell folliculitis
Unclassified cicatricial alopecia
(Lichen planus)

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Chapter 9

Male Androgenetic Alopecia

Andrew Messenger

9

Synonyms

male balding, male pattern balding, male pattern hair loss, male androgenetic alopecia

Key Features

- Male balding is a common androgen-dependent trait in which there is a progressive decline in the activity and size of scalp hair follicles.
- Male balding can cause significant adverse effects on psychosocial wellbeing in some men.
- The predisposition to male balding is genetically determined and is polygenic in nature.
- Dihydrotestosterone, a 5*α*-reduced metabolite of testosterone, is the androgen responsible for driving hair loss. The primary target of androgens within the hair follicle is probably the follicular dermal papilla.
- Topical minoxidil lotion and oral finasteride, an inhibitor of type 2 5*α*-reductase, are the only medical treatments of proven efficacy in male balding. They help to prevent or delay the progression of hair loss and can stimulate some regrowth of hair in some men.
- Redistribution of terminal hair, using surgical techniques such as hair transplantation, can produce effective cosmetic results in selected cases.

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9.1 Introduction

The evolutionary significance of male balding, if indeed it has one, is unknown. Current societal attitudes towards male balding vary between indifference and negativity. An example of the latter is the reported high frequency of an apparent full head of hair amongst members of the American House of Representatives [60]. It might be expected therefore that retention of scalp hair is advantageous. However, whereas balding is now seen as a feature of aging and declining vigour, it may have had quite different implications in our evolutionary ancestors, where only young men counted and amongst whom balding would have been relatively uncommon. Secondary sexual hair growth is undoubtedly involved in sexual signalling in other species; for example, the length and colour of the lion's mane influences reproductive success [67]. Balding is a marker of sexual maturity in humans and some other primates (Fig. 9.1), and although it appears later than some other changes in post-pubertal hair growth it may still develop early enough to influence mating behaviour. There is some evidence that balding men have slightly higher androgen levels than non-bald men [4, 12, 36]. Whether this translates into greater reproductive success is unknown and difficult to verify, but it is perhaps the most likely explanation for the survival of balding genes into modern man.

For those interested in the biology of human hair growth, male balding is a fascinating subject. It also fascinates the lay public – new treatments are virtually guaranteed considerable interest from the media. For some sufferers it can be a source of great anxiety and have an adverse effect on their quality of life. Few men enjoy going bald. The lengths to which they are prepared to go to do something about it vary, but there is little doubt that a one-off safe treatment that reversed or prevented balding would be taken up with enthusiasm.



Fig. 9.1 Male chimpanzee with androgenetic alopecia

9.2 History

It has been known since ancient times that eunuchs do not go bald. Hippocrates (Fig. 9.2) stated that "eunuchs are not subject to gout nor do they become bald" (Aphorisms VI, 28). The role of testosterone was first recognized by James Hamilton, an American anatomist [19]. He observed that men castrated before puberty retained a pre-pubertal hair line and did not go bald. Of 12 such men who were subsequently treated with testosterone, 4 developed typical male hair loss. Castration later in life halted the progression of hair loss but did not result in regrowth of hair.

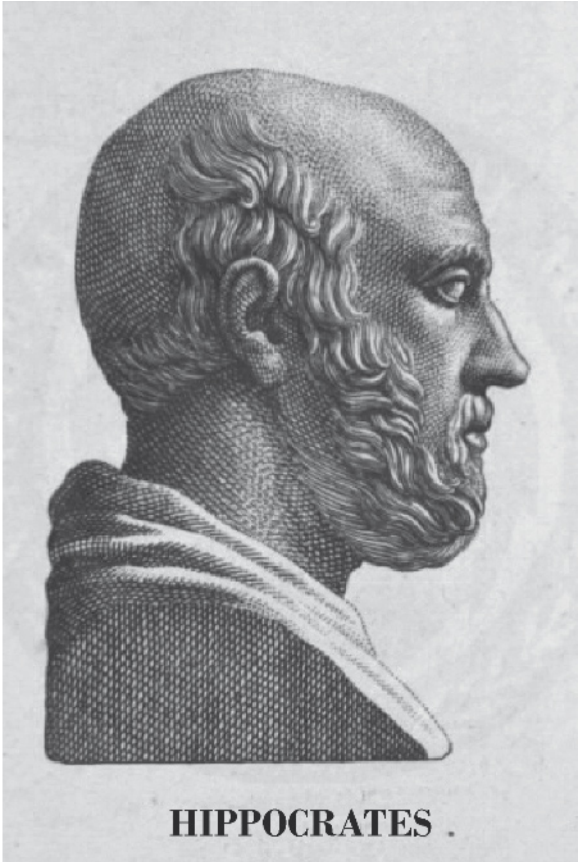


Fig. 9.2 Androgenetic alopecia in Hippocrates (Courtesy of the National Library of Medicine)

9.3 Aetiology

9.3.1 Androgens

There are still major gaps in our understanding of the aetiology of male balding. It is clear, however, that balding is an androgen-dependent trait, that it requires a genetic predisposition and that its severity and frequency in the population increase with advancing age.

Testosterone is the major circulating androgen in men. However, it is the more potent androgen dihydrotestosterone (DHT), the 5α-reduced metabolite of testosterone, that is responsible for driving hair loss. The conversion of testosterone to DHT is catalysed by the enzyme 5α-reductase. There are two isoforms of 5α-reductase, which are encoded by different genes [33, 63]. Although both enzymes catalyse the conversion of testosterone to DHT they differ in their pH optima, substrate affinities and tissue distributions. Type 1 5α-reductase is widely distributed in the skin [64], but expression of the type 2 isoform appears to be restricted to certain androgen target tissues such as the prostate, the epididymis and hair follicles in certain regions of the skin.

The biological role of DHT in hair growth first became apparent in studies of men with a genetic deficiency of type 2 5α-reductase (type II pseudohermaphroditism, pseudovaginal perineoscrotal hypospadias) [27]. In this autosomal-recessive disorder, genetic males (46XY) are born with normally differentiated, but usually undescended, testes. The external genitalia are ambiguous with a small hypospadic phallus, a bifid scrotum and a blind vagina. Partial virilization of the genitalia occurs at puberty, the voice deepens and the musculature assumes a typical male distribution. Circulating testosterone levels are within or above the normal male range but DHT levels remain low with testosterone:DHT ratios 3.5–5 times higher than normal. These men show a female pattern of androgen-dependent hair growth with terminal hair largely restricted to the axillae and the lower pubic triangle. In the large group of subjects studied in the Dominican Republic, beard growth was absent or sparse. More facial hair has been observed in affected men from other parts of the world, perhaps reflecting underlying racial differences in normal androgen-dependent hair growth, although this was reduced compared with normal males in the same communities [1, 28]. None of the cases studied has shown temporal recession of the hair line or balding. These observations were extended by the demonstration that treatment with a 5α-reductase inhibitor prevented the development of balding [57] or increased scalp hair growth [11] in macaques, a primate that reliably develops androgen-dependent hair loss. Confirmation of the importance of DHT in humans came from the results of large clinical trials showing that finasteride, an inhibitor of type 2 5α-reductase, prevents progression of balding in most men and stimulates some recovery of hair growth in about two-thirds [34]. This latter finding also illustrates that, contrary to Hamilton's conclusions from his observations in eunuchs, male balding is partially reversible.

Androgens act on tissues via binding to a specific intracellular protein, the androgen receptor, a member of the steroid-thyroid nuclear receptor superfamily [38]. In the presence of ligand, androgen receptors undergo a change in conformation, resulting in an activated form that binds as a homodimer with a specific androgen response element on the target gene. The hormone–receptor complex then activates transcription of target genes. A large number of proteins (co-regulators) regulate the activity of the hormone–receptor complex, both enhancing (co-activators) and suppressing (co-repressors) transcriptional activation. Mutations in the androgen receptor gene are responsible for the androgen insensitivity syndrome [53]. XY individuals with the complete form of the syndrome (CAIS, testicular feminization), in which there is failure of functional androgen receptor expression, have intra-abdominal testes but female external genitalia and body form, and female psychosexual development. After puberty circulating testosterone is in the normal or elevated male range but pubic and axillary hair fail to develop, and there is no beard growth or balding. Some pubic and axillary hair may be present in incomplete forms of testicular feminization.

A role for androgens in the aetiology of balding is incontrovertible. Nevertheless, other factors are clearly involved as not all men develop balding despite having similar androgen levels to those that do.

9.3.2 Genetics

Twin studies demonstrate that the predisposition to male balding is predominantly due to genetic factors [22, 45, 56]. Published concordance rates for monozygotic twins are around 80%–90%, with consistently lower rates in dizygotic twins. Several studies have shown that there is a high frequency of balding in the fathers of bald men. For example, Ellis and colleagues reported that 32 of 54 bald men (59.3%) had fathers with a greater degree of baldness, whereas only 1 of 65 sons of 50 non-bald controls had type III baldness or greater [14]. In a study involving 572 men aged 16–91, there was a significant increase in the risk of balding in young men with a balding father over those with a non-bald father [odds ratio (OR) 5.5, 95% confidence interval (CI) 1.26–23.99] which fell with increasing subject age to approach unity in elderly men [5]. The opposite trend was seen in non-

bald men, where the risk of non-balding in men with a non-bald father increased with age (OR 3.2, 95% CI 1.82–5.58 in subjects aged 70 and over).

From detailed family studies, Osborn suggested that balding is inherited in a Mendelian fashion, *B* and *b* representing the balding and non-balding alleles respectively [51]. She proposed that heterozygous and homozygous men develop balding whereas women need to be homozygous (*BB*). Several investigators have supported the idea that premature balding is due to the action of a single sex-influenced gene. Harris was able to fit men with premature balding into a model of monogenic inheritance although not those with late-onset balding [21]. Carey and colleagues described several families in which premature balding in male members appeared to denote carrier status for an autosomal-dominant gene responsible for polycystic ovarian disease in the women [6]. There was an association with one allele of the steroid metabolism gene CYP17, although this genetic change was not the primary cause of either condition [7]. However, others have disputed the concept of monogenic inheritance. From an analysis of the family histories of women with androgenetic alopecia, Smith and Wells concluded that balding is probably multifactorial [61]. This conclusion was strongly supported by Kuster and Happle in a detailed critique of the published data [37] and current thinking is that the predisposition to balding has a polygenic basis.

Attempts to identify the genes involved in male balding have been limited to a small number of candidate gene studies. No associations have been identified with 5α-reductase genes [14, 62] or the insulin gene [15]. However, three independent studies have found significant associations, both positive [17, 25] and negative [23], with variant regions of the androgen receptor (AR) gene. The AR gene is located on the X chromosome and men inherit it from their mother. This finding therefore confirms there is a maternal influence on male balding but does not explain the genetic contribution from the father.

9.3.3 Age

The population frequency and severity of male balding increase with age. Almost all Caucasian men develop some recession of the frontal hair line at the temples during their teens. Deep frontal recession and/or vertex balding may also start shortly after puberty although in most men the onset is later. Hair loss progresses to end-stage balding in 50%–60% of men by the age of 70. A small proportion of men (15%–20%) do not show balding, apart from post-pubertal temporal recession, even in old age. Some authorities have suggested that scalp hair loss in elderly men may develop independently of androgens (senescent alopecia) but this remains to be verified [35].



Fig. 9.3a,b Male pattern baldness with (**a**) frontotemporal regression and (**b**) vertex balding, Norwood Hamilton type IV vertex

9.4 Clinical Features

In the majority of men, balding is patterned, the two major components being fronto-temporal recession (Fig. 9.3a) and loss of hair over the vertex (Fig. 9.3b). This process may start at any time following puberty although in cases of very early onset hair loss is more commonly diffuse in nature. Hairs become shorter and may, although not always, become finer in calibre. Ultimately this may lead to complete hair loss except at the lateral and posterior margins of the scalp where hair is retained. In elderly men hair may also be lost in these parts of the scalp. Hamilton classified male balding into several stages [20] and his classification was subsequently revised by Norwood [44] (Fig. 9.4) although, as Norwood pointed out, the patterns of balding are infinitely variable and no single classification is applicable to all. A small proportion of men show a diffuse pattern of hair loss over the crown and frontal scalp with retention of the frontal hair line, similar to female pattern hair loss. This pattern occurs more commonly in oriental men. Paik and colleagues reported that 11.1% of balding Korean men showed a female pattern (Fig. 9.5) (cf. 2%–3% in Caucasians) [52].

The diagnosis of male balding is usually easy. Other causes of diffuse hair loss, such as diffuse alopecia areata or systemic lupus erythematosus, occasionally cause difficulties. Diffuse alopecia areata usually progresses more rapidly than male balding and a "tug test" is often strongly positive. Where doubt remains a biopsy may be necessary.

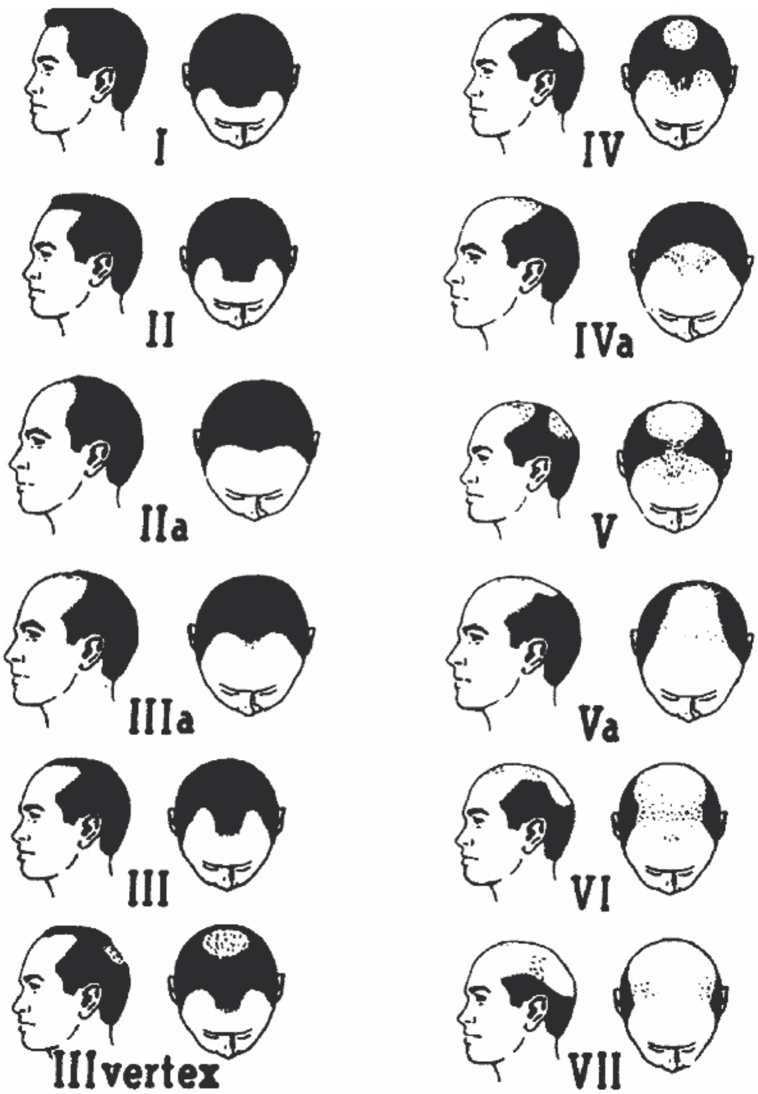


Fig. 9.4 Norwood's classification of male balding [44]



Fig. 9.5 A 38-year-old male patient with androgenetic alopecia of female type

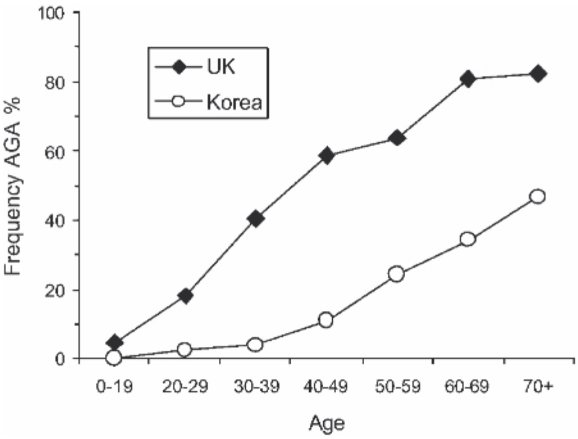


Fig. 9.6 Prevalence of male balding in British and Korean men [5, 52]

9.4.1 Prevalence

Balding occurs in all races but with differing frequencies (Fig. 9.6). The prevalence is highest in Caucasoids, reaching around 80% in men aged over 70 [5, 20, 44]. Setty reported that retention of a full head of hair is four times more frequent in African-Americans [58]. The prevalence in oriental races is also lower than in Caucasian men [52].

9.5 Pathophysiology of Male Balding

There are two elements to the changes in hair growth during balding. First, hair follicles become progressively miniaturized over the course of successive hair cycles. This is a global change in the dimensions of the follicle, which becomes narrower and shorter and produces a hair of smaller diameter. Second, there are changes in the hair cycle. Courtois and colleagues studied the hair cycle on the scalp in a group of male subjects over a period of up to 15 years, using phototrichograms [9]. In all the subjects there was a progressive reduction in the mean duration of anagen over the study period. The length of time for which a telogen hair was retained in the follicle remained unchanged but the period when the follicle was empty, referred to as the latent period, became longer. These changes were more pronounced in balding subjects. The combined effect of follicular miniaturization and changes in the hair cycle is a reduction in the length and diameter of hairs and a reduction in hair density. During the development of balding the relative contributions of these two components vary between individuals. In some men the major change is follicular miniaturization with little or no reduction in hair density whereas in others prolongation of the latent phase of the hair cycle appears to predominate.

The success of hair transplantation demonstrates that the specificity of the response of hair follicles to androgens is determined within the skin. Hair follicles in occipital skin, a site which shows little or no response to androgens, retain their site-specific behaviour when transplanted into balding areas on the frontal scalp [50]. Conversely, hair follicles from balding scalp continue to regress when transplanted into skin of the forearm [43]. The development of micrografting, in which individual follicles are transplanted, shows that androgen responsiveness is determined at the level of the follicle or its immediate tissue environment.

It is currently thought that the hair follicle dermal papilla is the primary target of androgen action [55]. The dermal papilla plays a key role in regulating hair growth [46] and its volume probably determines the size of the hair follicle [13, 66]. Dermal papilla cells express androgen receptors, unlike the majority of follicular epithelium, and in androgen-dependent regions also express type 2 5α-reductase [3, 30]. In vitro studies using systems in which dermal papilla cells are co-cultured with cultured hair follicle cells have shown that dermal papilla cells derived from balding scalp release transforming growth factor-β, a known inhibitor of hair growth, when incubated with testosterone [29]. In contrast, dermal papilla cells from beard skin, where androgens have a stimulatory effect on hair growth, release insulin-like

growth factor-1 (IGF-1) when cultured under the same conditions [31]. Hence, the site specificity of androgen-dependent hair growth may be due to differences in the balance of stimulatory and inhibitory growth factors produced by the dermal papilla in response to androgens.

9.5.1 Histopathology

The main histological feature of male balding is an increase in the absolute number and proportion of small vellus-like (miniaturized) hair follicles [68]. This is most readily seen in horizontal sections. The ratio of terminal to vellus-like follicles in normal scalp is at least 7:1. In pattern hair loss, in both women and men, this ratio falls to less than 3:1. The proportion of follicles in the telogen stage of the hair cycle is also higher than in normal scalp.

A perifollicular lymphohistiocytic infiltrate around the infundibulum and sebaceous duct is a common feature of male balding and this may be associated with thickening of the perifollicular connective tissue sheath. These findings have led to the suggestion that inflammatory factors are involved in the pathogenesis of male balding [32]. However, perifollicular inflammation around the lower infundibulum is also seen in non-balding scalp and balding is not obviously affected by treatment with anti-inflammatory or immunosuppressive drugs (except for ciclosporin, which has a general hypertrichotic effect not limited to the scalp).

9.6 Psychosocial Effects of Male Balding

The adverse effects of male balding are predominantly psychosocial in nature [8]. Balding men who seek medical advice will inevitably be unhappy about their hair loss. An Italian study found a high frequency of personality disorders amongst such men [40], suggesting that those presenting to physicians are inherently less able to cope with what they see as a departure from normality. Thus, concerns about hair loss may reflect a general anxiety about other difficulties relating to self-worth. Nevertheless, studies in unselected groups of men suggest that balding causes increased stress, lowered self-esteem and reduced satisfaction with body image in the population at large. These feelings have some validity. Controlled studies have found that independent observers rate bald men as older and less attractive than non-bald men, though whether bald men are truly disadvantaged by these perceptions is unknown.

Concern about hair loss tends to be most pronounced in young men, at a time in life when physical attractiveness can seem a vital issue. However, in a society that places great value on retention of youthfulness, a concept reinforced on a daily basis by the advertising media, it is by no means restricted to this group. Men concerned by hair loss are often embarrassed to seek help, particularly from the medical profession where balding may be seen as a trivial problem. One hopes that the advances in our understanding of the effect of male balding on quality of life and the issues surrounding it, and the advances in treatment, will see a change in this attitude.

9.7 Associated Pathologies

9.7.1 Coronary Heart Disease

Several studies have reported an association between coronary heart disease and male balding. In the largest of these, a retrospective study conducted amongst 22,071 US male physicians [39], there was a weak association between coronary heart disease and vertex balding. A prospective study in 2017 men from Framingham, Massachusetts found an association with the progression of balding but not with its extent [24], and a case–control study from Finland reported an association with early-onset balding [41]. In a study from Australia, Ellis and colleagues [16] found no difference in the frequency of established risk factors for coronary heart disease between bald and non-bald men, suggesting that balding predisposes to heart disease through yet undefined mechanisms. The link with male balding is much weaker than for other risk factors in coronary heart disease and some have cast doubt on its existence [18].

9.7.2 Prostate Cancer

Like male balding, androgens are involved in the aetiology of prostate cancer. Studies looking for possible associations between male balding and prostate cancer have given mixed results. Two case–control studies from the USA [10] and Greece [26] found no difference in the frequency of balding between men with prostate cancer and control subjects. However, using a similar approach, a larger Australian study reported an association between balding and prostate cancer with an adjusted odds ratio of 1.54. In a prospective study from the USA a group of 4421 men were followed for up to 20 years. There was an increased frequency of prostate cancer (OR 1.5) in men who were balding at baseline and this appeared to be independent of other risk factors.

Whilst they were unable to demonstrate an association between prostate cancer and balding, Drake and colleagues found an increase in the level of serum free androgens in both groups compared to unaffected controls [12], suggesting a common pathway in the aetiologies. This has been supported by the report of a reduced risk of both metastatic prostate cancer and male balding in men carrying the E211 G>A androgen receptor polymorphism [23].

9.8 Management

Male balding is a biologically normal process. Under normal circumstances it has no adverse effect on physical wellbeing apart from increasing the risk of chronic photodamage to unprotected scalp skin. Under exceptional conditions a full head of hair may also contribute to thermoregulation: the French military surgeon Dominique-Jean Larrey observed that the bald men (and men without hats) were the first to die during the Russian campaign in the winter of 1812. Yet balding still has a powerful effect on the human psyche, to the extent that few men would choose to go bald were the choice available. Many men accept loss of their hair and prefer to let nature take its course. However, for some men balding is important enough for them to seek treatment and for a few concern about hair loss reaches the level of a body dysmorphic disorder. It is important to recognize men in the latter group, as treatment aimed at addressing the perceived hair problem is unlikely to be successful. A number of studies have shown that male balding has an adverse effect on quality of life (though this is almost inevitable in those seeking professional advice). Nevertheless, balding is often seen as a trivial issue (mainly by non-sufferers) which may make men reluctant to approach their physician as they perceive, rightly or wrongly, that they will not receive a sympathetic response.

9.8.1 Counselling

Men seeking medical advice for male balding fall roughly into three groups (which may overlap): those who wish to ensure their hair loss is not a manifestation of an underlying serious disease, those who wish to be treated and those with a body image problem. For all groups counselling should include an explanation of the nature of male balding and its natural history. For those interested in preventing further progression or improving their hair status the treatment options will also need to be discussed. For those with a body dysmorphic disorder involvement of a clinical psychologist or psychiatrist should be explored. Hair loss is an emotive issue and sufferers are vulnerable to exploitation by the unscrupulous. Patients should be advised against parting with large sums of money on unproven and valueless remedies.

9.8.2 Medical Treatments

At present only two medical treatments, minoxidil and finasteride, are of proven benefit in male balding. Both drugs will stimulate some regrowth of hair in some men but are perhaps better regarded as preventative treatments. Neither will regrow hair on completely bald scalp and continued treatment is necessary to maintain the response. Both drugs have a good safety record, a consideration of paramount importance when treating hair growth disorders.

9.8.2.1 Minoxidil

Minoxidil was licensed as an oral drug to treat hypertension in the early 1970s. It soon became apparent that a high proportion of those taking minoxidil tablets developed significant hypertrichosis, a side-effect that has almost eliminated its use as an anti-hypertensive agent. Following a report of increased hair growth on the scalp of a balding man taking minoxidil tablets [69], extemporaneous formulations of minoxidil lotion were developed for topical application in the treatment of hair loss (initial reports concentrated mainly on alopecia areata). A 2% formulation of minoxidil lotion was subsequently licensed by the American Food and Drug Administration for the treatment of male balding and marketed by the Upjohn Company in 1986. A 5% formulation was marketed in 1993. The recommended dose is 1 ml twice daily (for both 2% and 5% formulations).

The mechanism of action of minoxidil on hair growth is uncertain [42]. There is convincing evidence that its vasorelaxant activity is due to opening of ATP-sensitive potassium channels (K_{ATP} channels) in the sarcolemma of vascular smooth muscle cells. There is circumstantial evidence that its effect on hair growth is also due to opening of K_{ATP} channels but direct proof is lacking and it is unclear how this action modulates hair growth. The rapid response of hair growth to minoxidil suggests that the drug acts mainly to promote entry into anagen of follicles in a latent stage of the hair cycle. There is no convincing evidence that minoxidil reverses follicular miniaturization although it may prevent or delay it.

Clinical trials using various endpoints, including hair counts, hair weight and global photography, have confirmed improvement in male balding with the use of minoxidil lotion [48, 54]. The mean increase in target area

hair counts is about 8% with 2% minoxidil lotion and 10%–12% with the 5% formulation. When assessed by global photography nearly 60% of men show improvement with 5% minoxidil lotion and 40% with 2%, compared to 23% with placebo. The response to minoxidil in terms of increased hair counts and hair weight is rapid and peaks by 16 weeks although the cosmetic response may take longer to become apparent. Trials continued for up to 2 years suggest the improvement is sustained providing treatment is maintained. Any positive effect on hair growth is lost within 4–6 months of stopping treatment [47, 54].

Adverse effects of minoxidil are mainly dermatological. Constituents of the vehicle occasionally cause scalp irritation, more commonly with the 5% formulation. Allergic reactions to minoxidil or propylene glycol (a component of the vehicle) are rare but necessitate stopping treatment. Some patients notice an increase in hair shedding 2–8 weeks after starting treatment. This is self-limiting but patients should be forewarned not to stop treatment if this happens.

A new topical foam preparation containing 5% minoxidil has recently been approved for use in men by the USA Food and Drug Administration. It is less messy than the current lotion formulation and is potentially less irritant as it does not contain propylene glycol. The results of clinical trials are awaited.

9.8.2.2 Finasteride

Finasteride is a competitive inhibitor of type 2 5α-reductase. Taken orally it reduces DHT levels in serum and in scalp by up to 70% [12].

Large-scale and long-term placebo-controlled studies using hair count and global photographic technology show that finasteride (1 mg daily) prevents or slows the progression of male balding in most men and about two-thirds experience some improvement [34]. The improvement peaks at around 12 months and, on average, there is some decline after 2 years. However, after 5 years those on placebo continued to lose hair more rapidly than those on finasteride [59].

Clinical trials have shown a small increase in sexual dysfunction (e.g. impotence) in men taking finasteride for male balding (4.2% versus 2.2% for placebo in young men [34], 8.7% versus 5.1% in older men [12]). These side-effects resolve on discontinuation of the drug. The level of finasteride in semen is very low and poses no risk to a male fetus in a pregnant sexual partner. Data from a long-term trial in 18,882 men aged over 54 taking 5 mg finasteride daily or placebo showed a 25% overall reduction in the incidence of prostatic cancer in those taking finasteride but a small increase in the frequency of high-grade prostatic cancer [65]. The relevance of this finding to men taking 1 mg daily for male balding is unknown but it is advisable to warn patients of this uncertainty.

9.8.2.3 Minoxidil versus Finasteride

There are no blinded controlled trials comparing the response of male balding to minoxidil lotion and oral finasteride although one open study reported a greater degree of improvement in men taking finasteride compared to those using 5% minoxidil lotion [2]. In practice the decision comes down to patient preference. On the one hand, minoxidil is a little cheaper and it has been in use for longer so more is known about long-term safety. On the other hand, it is more convenient to take a single tablet of finasteride daily than apply a lotion twice daily to the scalp.

We do not know whether the combination of minoxidil and finasteride confers any advantage over either drug used singly. The mechanisms of action are different so, on a superficial level, one might expect at least a partially additive effect. However, their outcomes in terms of their effects on the dynamics of hair growth are probably the same.

9.8.3 Surgery

Surgical treatment of male balding involves the redistribution of terminal hair to cover balding scalp – the number of terminal hair follicles on the scalp remains the same. In most cases this means transplanting hair follicles from the occipital scalp to the balding areas. Other techniques, such as excising the balding skin (scalp reduction) and rotational flaps are now less widely used. Surgical treatment can achieve very satisfactory results but careful patient selection and surgical skill allied to the aesthetics of scalp hair growth are essential. A detailed review of the indications and techniques of hair surgery is beyond the scope of this article (see Chap. 22). However, key considerations include the following [49]:

- There should be an adequate donor area, i.e. good hair density in the occipital scalp
- Age: the predictive value for men aged <25 is very uncertain. Surgery in young men may result in misplaced hairlines or an unnatural appearance 20–30 years later as balding progresses
- Correction of established frontal hair loss is more effective than vertex balding, which tends to progress with time
- Thicker hair shafts give better coverage than fine calibre hair. In Caucasians, fair hair gives a more natural appearance than dark hair (which exaggerates the contrast with the colour of scalp skin)

Experienced surgical teams can give significant improvement after one to two sessions. The final results take 5–6 months to become apparent.

Complications of surgery include scalp erythema and crusting, and facial oedema. Less common problems include infection, post-operative bleeding, scarring and arterio-venous fistula formation.

9.8.4 Cosmetics

Hair styling is perhaps the simplest approach to modifying the cosmetic impact of male balding. Currently fashionable short hair styles are particularly effective in minimizing the contrast between balding and non-balding regions of the scalp. Some men resort to wigs or toupees. While these give an instant result a natural appearance demands skilled professional input.

Summary for the Clinician

As an entirely natural process with no significant detriment to physical health it can be argued that society should not devote scarce resources to understanding the causation of male balding or its treatment. Yet, despite its apparent inconsequentiality male balding remains a source of fascination to hair biologists, to comedians, to the public at large, and a source of discontent to those who experience it. Disorders of hair growth, in general, promote strong adverse sentiments to the extent that perceptions of normal hair growth seem almost "hard-wired" into the human psyche. For those who deal with male balding at a professional level it is therefore important to appreciate the deleterious effect it can have on quality of life. It is probably true to state that almost all men would welcome a one-off treatment that was cheap, safe and effective. However, we are a long way from realizing this ideal. At present there is considerable interest in the possible application of cell culture techniques for treating male balding. This concept envisages the expansion of populations of hair follicle precursor cells in vitro, and then re-implanting these cells into balding scalp. This approach may eventually provide the answer but there are many hurdles to overcome before this is a practical reality. The other approach would be to modify the public perception of balding, so that it is no longer seen as relevant. This culture shift would perhaps be even more difficult to achieve.

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Chapter 10

Female Pattern Hair Loss

10

Elise A. Olsen

Synonyms

female pattern hair loss, androgenetic alopecia, androgenic alopecia, common baldness in women, diffuse alopecia in women, female pattern baldness, diffuse hormonal alopecia

Key Features

- Decrease in hair density in the central (vertex, mid and frontal) scalp, bitemporal and parietal regions in women.
- Miniaturization of affected hairs.
- Two ages of onset: early (post-puberty to third decade) and late (age 40+ years).
- Signs of hyperandrogenism (hirsutism, irregular periods) or hyperandrogenemia occur in a subset of women with female pattern hair loss (FPHL) but most women with FPHL have neither.
- Many, but not all, affected women respond to antiandrogens or 5α-reductase inhibitors with increased hair growth indicating an androgen etiology in at least some cases of FPHL.

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10.1 Introduction

Female pattern hair loss (FPHL) is a broad term for the decrease in central scalp hair density that occurs in many females post puberty [62]. Many other terms have been used for this particular type of alopecia including androgenetic alopecia (AGA) and androgenic alopecia, both terms which imply a specific androgen-related and genetic etiology. While certainly a proportion of women with this hair phenotype have the female counterpart of male AGA, i.e., they clearly respond with hair growth to antiandrogens or 5α-reductase inhibitors, it has not been proven that all women with this pattern of hair loss clearly have an androgen-related process [62]. Therefore, the term FPHL, while inclusive of AGA in women, allows for further thought and research on this hair loss condition without implying causality.

FPHL affects >50% of women over the age of 50 years and while the hair loss may seem trivial to the observer, it is often emotionally devastating for the affected women. FPHL may occur alone or may be part of a constellation of androgen-related conditions. The diagnosis of FPHL is not clear-cut as it is in men with male pattern hair loss (MPHL) but requires a history, physical exam, laboratory work, and often a scalp biopsy to differentiate it from other causes of hair loss. Current treatments for FPHL are limited in number and degree of efficacy.

10.2 History

Beek in 1950 noted that baldness and calvities frontalis in women increased dramatically from the fourth to the sixth decades [6]. In his 1951 review of 214 Caucasian women, Hamilton noted that this hair loss in women never progressed further than a pattern IV (see Chap. 9) and that in most cases only to a pattern II limited to bitemporal recession [39]. Although he showed that MPHL was androgen related [38] he questioned whether androgens were clearly causal in FPHL [39]. Maguire and Kligman in a seminal article on common baldness in 1963 [52] and Ludwig in 1964 [50] claimed that male and female pattern hair loss had the same etiology (genetic predisposition and androgen stimulation) but that women did not usually have frontotemporal recession as seen commonly with men. Ludwig in 1977 described the progressive centrifugal hair loss with preservation of the frontal hair line to which he assigned three pictorial gradations of severity [51] (Fig. 10.1). Olsen commented on the frequent Christmas tree pattern of FPHL with frontal accentuation [59, 61, 69] (Fig. 10.2). Ludwig suggested the term "female type of androgenetic alopecia" to include causality, but more recently a consensus meeting of specialists in hair and reproductive endocrinology proposed the term FPHL to describe the hair phenotype in women with or without an obvious androgen relatedness [62].



Fig. 10.1 Ludwig patterns of hair loss (reprinted with permission from Olsen [62])



Fig. 10.2 Woman with frontal accentuation of hair loss

10.3 Epidemiology

The comparative prevalence of the three clinical patterns of FPHL (Fig. 10.3) is unknown. However, Hamilton [39] noted a male pattern of deep frontotemporal recession usually with some loss of the midfrontal border of the scalp in 19% of women with no increase in those over the age of 50. Olsen [61] noted a frontal accentuation pattern but usually with preservation of the frontal hair line in 48% of women age 15–70 presenting to clinic with FPHL (Fig. 10.4). The Ludwig pattern of FPHL has more commonly been used to examine the prevalence of FPHL but the information on prevalence using this has varied widely. Venning and Dawber found that 87% of 254 premenopausal women and 63% of 310 postmenopausal women without specific complaints of hair loss had Ludwig I-III hair loss [104]. These percentages seem unusually high for young women and Birch et al. in evaluating 377 women presenting to a dermatology clinic with complaints unrelated to hair loss reported a 6% incidence of the Ludwig pattern in women under the age of 50 years and 38% in women ≥70 years [8]. Norwood confirmed the increasing incidence of FPHL with age although no description of the criteria for the diagnosis was given: 14% of 568 women under 50 years old compared to 26% of 438 women over 50 years old [57]. Gan and Sinclair (Fig. 10.5) used a photographic scale to pictorially grade FPHL hair loss and determined that 53 of 267 (20%) of women under 50 had FPHL (defined as >Stage II) compared to 90/450 (42%) of women over 50 [32]. Clearly, there are racial differences with less FPHL reported in women of oriental compared to European descent [75]. The incidence of FPHL in women of African descent is difficult to determine, at least in the United States, secondary to the frequent overlap of central centrifugal cicatricial alopecia [65].

10.4 Pathophysiology

10.4.1 Androgens

Circulating androgens in women come from three potential sources: adrenal, ovary, and peripheral conversion. Availability in the hair follicle of testosterone (T) and dihydrotestosterone (DHT), the primary androgens causing cellular androgen-related effects, depends on an intact central (gonadal or adrenal) steroid biosynthetic pathway that will take synthesis to at least dehydroepiandrosterone sulfate (DHEA-S) (Fig. 10.6) [41] as well as the presence of the terminal conversion enzymes of steroid sulfatase, 17β-hydoxysteroid dehydrogenase, 5α-reductase, and 3β-hydroxysteroid dehydrogenase. All these enzymes are potentially available in the follicle itself [16]. Androgens circulate in the blood either free or preferentially bound to sex-hormone-binding globulin (SHBG) (78%), albumin (20%) or cortisol-binding globulin or acid α-2 glycoprotein (<1%) [1]. The final metabolite of DHT, 3α-androstanediol glucuronide, is dependent on the enzyme 3α-hydroxysteroid dehydrogenase.

The ultimate determinant of what androgen action will take place in a given tissue is dependent on the amount and type of androgen delivered to the tissue, the amount and type of androgen synthesized in the tissue, the amount of local androgen receptor, and the relative binding affinity to the androgen receptor of the androgens present in the tissue and their relative metabolism. The circulating androgen levels are largely age dependent, both adrenal and gonadal sources increasing with puberty and decreasing with age beginning in the fourth decade [12]. In postmenopausal women, almost 100% of androgens come from interconversion of adrenal dehydroepiandrosterone (DHEA) or DHEA-S in peripheral target tissue [47]. The amount of T and DHT is also

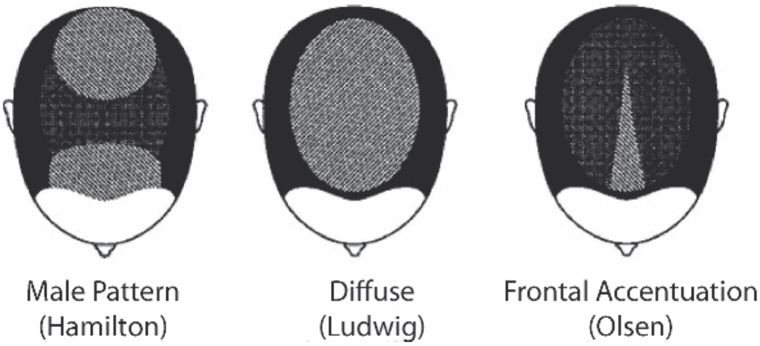


Fig. 10.3 Patterns of hair loss in female pattern hair loss (reprinted with permission from Olsen [64])

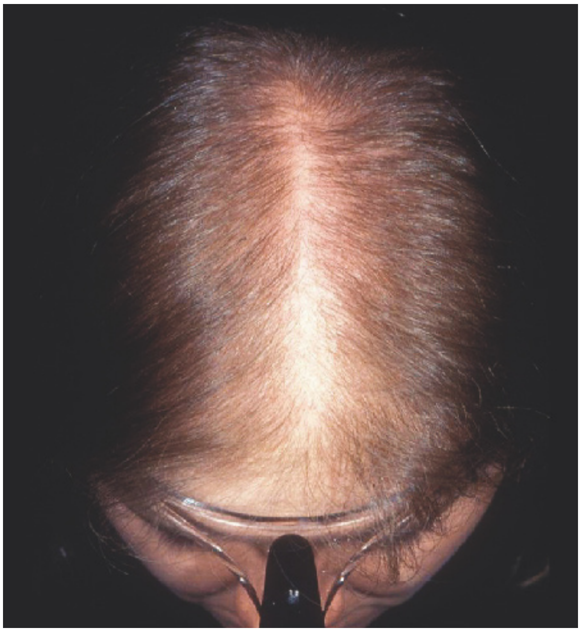


Fig. 10.4 A 42-year-old woman with mild but obvious female pattern hair loss

affected by the enzyme aromatase, which converts T to estrogen, thus decreasing both circulating and tissue T and DHT. Aromatase further affects the delivery of androgens to peripheral tissue since estrogen increases SHBG, thus decreasing unbound T/DHT [1].

The amount of 5α-reductase is tissue specific and has been shown to be increased in hairs from male balding scalp [7, 85], in balding versus nonbalding scalp of men with MPHL [78, 83] and to lead to increased DHT in hairs from balding versus nonbalding men [17]. However, the only study to evaluate 5α-reductase in FPHL is that of Sawaya and Price [83], which showed increased 5α-reductase in the frontal compared to occipital scalp but less 5α-reductase in all areas of the scalp of women compared to men [7].

From the clinical documentation and observations of increased hair growth in clinical trials of the 5α-reductase inhibitors finasteride [45, 80] and dutasteride [70], it is known that most male pattern baldness is androgen, and specifically DHT, dependent. However, the negative results of a one-year multicenter placebo-



Fig. 10.5 Photographic grading scale for female pattern hair loss (reprinted with permission from Gan and Sinclair [32])

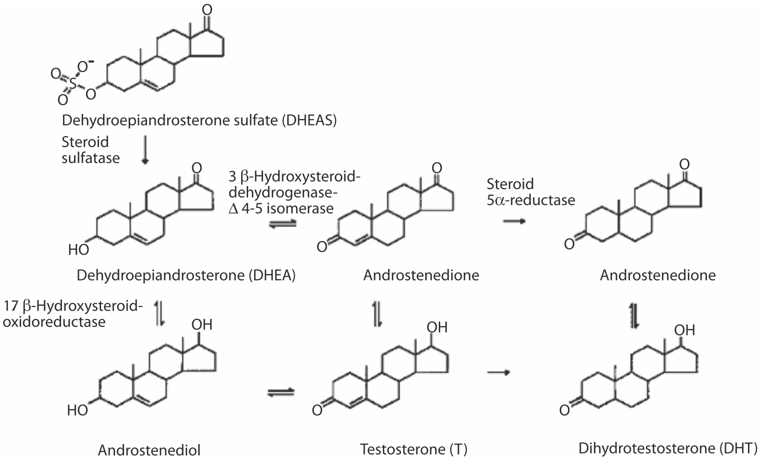


Fig. 10.6 Patterns of cutaneous androgen metabolism and the converting enzymes (reprinted with permission from Hoffmann et al. [41])

controlled clinical trial of finasteride in post-menopausal women with Ludwig I or II FPHL refute the assumption that DHT is responsible or involved in the hair loss process for all women with FPHL [77]. This study sparked a reassessment of the potential androgen relatedness, whether T or DHT, in all subgroups of FPHL. Vierhapper reported, using a stable isotope dilution method and mass spectrometry, that although the production rate of DHT was increased in men with MPHL compared to male controls without hair loss, that DHT production was low to normal in women with FPHL compared to controls [106, 107]. Futterweit et al. found that 61.5% of 109 women aged 14–47 (mean age 32) with moderate to severe (primarily early onset) FPHL, did not show biochemical evidence of androgen excess as measured by DHEA-S, androstenedione, DHT, and free T [31]. Furthermore, if one removed the women with irregular periods or hirsutism from this study, then 84% of the women with FPHL without any overt clinical signs of hyperandrogenism also had no biochemical evidence of androgen excess. Schmidt et al. found no increase in androgens in 46 premenopausal females with Ludwig I or II AGA without hirsutism or menstrual disturbances [84]. Birch et al. also found that hyperandrogenemia occurred only in the women with FPHL who also had a clinical sign of hyperandrogenism such as hirsutism [9]. Decreased SHBG has been reported in women with FPHL, which may lead to a decrease in free androgen index (T/SHBG) but this has not been a consistent finding [9, 64]. No correlation of the degree of FPHL was seen with a specific marker of androgen activity, in this case increased sebum secretion [113], and late-onset FPHL specifically occurs at a time when the serum concentrations of all androgens, including DHT, T, androstenedione, dehydroepiandrostenedione and dehydroepiandrostenedione sulfate, are diminishing [12]. FPHL has been reported in a woman with complete androgen-insensitivity syndrome (i.e., no androgen receptor) [113] and in a woman with hypopituitarism without any circulating androgens or gonadotropins [74]. In a controlled trial, cyproterone acetate, an antiandrogen, was not effective in FPHL except (and then only minimally) in the subgroup of women with elevated body mass index (BMI), low SHBG and increased free androgen index [105].

On the other hand, there are undoubtedly some women with FPHL, particularly younger women, who have an androgen-dependent process. Of 89 consecutive premenopausal women age 27–36 years old with FPHL referred to a reproductive endocrinology service, 24% had irregular periods and 21% had hirsutism [15] compared to 20% and 27% respectively reported by Futterweit et al. [31].

However, surprisingly, despite normal blood androgens in the great majority of women, 67% of 89 women reported by Cela et al. were determined by pelvic ultrasound to have polycystic ovarian syndrome (PCOS) in comparison to 27% in a control population [15]. Futterweit et al. [31] noted PCOS in a smaller percentage of women with FPHL, 28% of 109 patients, with 23% of these PCOS cases presenting without either oligomenorrhea or increased serum androgens. PCOS is the most common cause of hirsutism [3] and is not only associated with elevated androgens but also with other abnormalities including insulin resistance. Carey et al. suggested that PCOS and MPHL segregate as an autosomal-dominant phenotype with other genes modifying the expression of that phenotype [13].

Women with late-onset FPHL with [87] and without [92, 97] hyperandrogenism and women with early-onset FPHL without hyperandrogenism [42] have been reported to respond to the decreased DHT induced by finasteride. It may be that the negative placebo-controlled trial in postmenopausal women, which primarily included women with late-onset FPHL and did not stratify subjects by signs or biochemical evidence of hyperandrogenism, collapsed the results for two different types of FPHL, one that is androgen dependent and one that is not [77]. Certainly, the issues of DHT and 5α-reductase in all type, of FPHL, both early and late onset and with or without hyperandrogenism, deserve further exploration.

10.4.2 Estrogens

The hair follicle has estrogen receptors, potentially making it an estrogen-sensitive organ. Like androgens, estrogens are produced both by the gonads and by other tissues including the hair follicle. As with androgens, the precursor hormones (in this case androstenedione and T), the enzymes involved in estrogen production (aromatase and 17-hydroxysteroid dehydrogenase), and the hormone receptor [estrogen receptor (ER)] are present in the follicular tissue [18, 93]. There are two types of ER in humans – ERα, which is primarily an activator of transcription but which is poorly expressed in hair follicles, and ERβ, which generally suppresses cellular functions and is expressed in many parts of the hair follicle. In animals, estrogen primarily inhibits hair growth but its effect in humans is not as clear. In vitro experiments suggest that estrogen inhibits elongation of hairs from the female occipital scalp but studies by this same group using male frontotemporal hairs show stimulation of hair growth with estrogen [19]. Differences in estrogen's effects in various tissues are likely related to differences

in the tissue distribution of the type of ER and/or to the tissue levels of co-regulatory proteins [79]. Estrogen levels have been shown to decrease in women with early-onset FPHL compared to controls [106]. Estrogen has been shown to have an effect on androgen-related growth of secondary sexual hairs [84] and may affect the amount of DHT in tissue by its effect on 5α-reductase and/or the conversion of T to weaker precursors [56]. How (or whether) estrogen may affect hair growth in FPHL has yet to be determined.

10.4.3 Genetics

The genetics of FPHL is also unclear. A family history of hair loss is common but the lack of one does not rule out the diagnosis. In women with FPHL, the incidence of pattern hair loss in those first-degree male relatives >30 years old was 54% and in female relatives over 30 years old was 21% [91]. The androgen receptor is on the X chromosome, which could explain the mosaic effect on the hair follicles in the involved scalp in women with FPHL versus an effect on all follicles in the involved scalp in men with MPHL. However, men with MPHL have a strong paternal history of MPHL which does not support an X chromosome inheritance for both male and female pattern hair loss. It is likely that early and late FPHL are distinct genetically and that the cause of FPHL is polygenic and multifactorial.

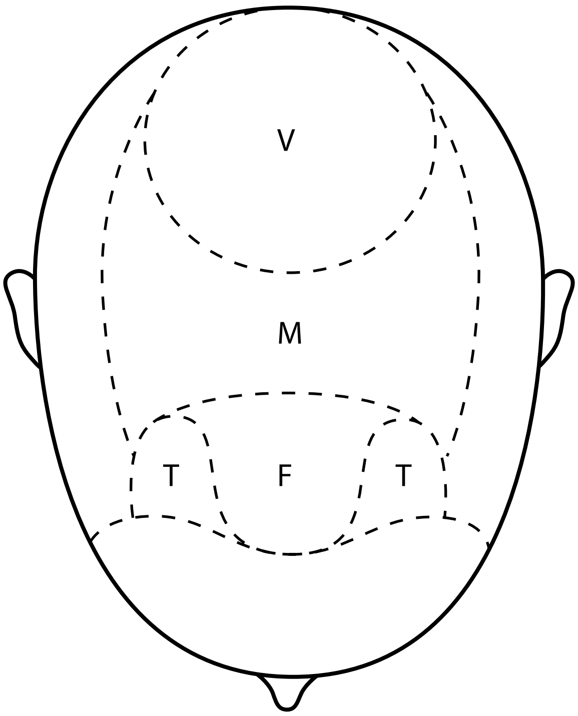


Fig. 10.7 Regions of the scalp potentially involved in pattern hair loss. (*F* Frontal, *M* mid, *T* temporal, *V* vertex) (reprinted with permission from Olsen [63])

10.5 Clinical Features

The hair loss in FPHL involves the same general areas of the scalp as in MPHL (Fig. 10.7) but the final extent of loss in the various regions of the scalp is less. Mild bitemporal recession, which in women implies finer and shorter hairs [52] versus balding as in MPHL, has been noted to occur in 60% [39] to 64% [32] of women and to increase with age [104]. Although it may be associated with the other areas of hair loss seen with FPHL, bitemporal recession may occur alone or in association with chronic telogen effluvium (CTE).

There are two main ages of onset of FPHL, one in the immediate post-puberty period to the third decade, much like that of MPHL, and a second peak in the fifth and early sixth decade [62]. Women with early-onset FPHL are much more likely to have an associated hyperandrogenism and clear-cut AGA than those with late-onset FPHL. The late-onset FPHL often corresponds temporally to perimenopause or menopause but hormone replacement therapy with estrogen does not reverse this process. There is an age-related decrease in hair density [5, 9, 63, 69] that is always greater on the central scalp and that overlaps and undoubtedly contributes to the hair loss of late-onset FPHL.

The hallmark of FPHL, as in MPHL, is an increase in miniaturized hair in the affected scalp. Two factors have been proposed to cause this miniaturization of terminal hairs: a shortening of anagen (which leads to shorter hairs and an increased percentage of hairs in telogen) and a smaller dermal papillae/hair matrix which leads to a transformation from terminal to vellus hair diameter. This is mirrored in the typical histopathological findings on scalp biopsies of an increase in telogen hairs and vellus-like hairs compared to normal [110]. The accompanying age-related decrease in hair diameter is not race specific [43, 98]. In women, as opposed to men, with pattern hair loss, this miniaturization process does not progress to baldness because all hairs in the affected areas of the central scalp are not equally affected and the miniaturization is not as profound.

Early in the process of FPHL, there may be an increase in hair shedding which on clinical exam is manifest as a positive telogen hair pull in affected areas. However, over time, this hair shedding tends to stabilize and a hair



Fig. 10.8 Focal atrichia. Note the pencil eraser sized areas of hair loss

pull may not be positive even in the most profound examples of FPHL. This lack of shedding may be because of two factors. First, a lag phase at the end of telogen that delays the onset of a new anagen phase is seen in both male and female pattern hair loss [21, 37]. This lag phase would account for the affected follicles remaining empty for much longer than the usual telogen phase. Second, the decreased shedding could result from the overall decreased density of terminal hairs as it is only shedding of terminal hair that causes patient consternation and/or is assessed on the hair pull evaluation.

This lag phase may be related to a specific clinical clue to the diagnosis of PHL, i.e., the presence of what Olsen has termed "focal atrichia" or small eraser-sized areas of baldness [36, 37, 59, 99] (Fig. 10.8). Olsen and Whiting have found this focal atrichia to be a relatively specific clinical finding in late versus early FPHL and to be histologically characterized by a decrease in density of both terminal hairs and follicular units (E.A. Olsen; unpublished information). A brown halo at the base of the affected follicles has been noted as a clinical clue to pattern hair loss (peripilar sign) in both men and women [25]. This may relate to the common histopathological finding of chronic inflammation in pattern hair loss and could represent post-inflammatory hyperpigmentation.

10.6 Histopathology

Both MPHL and FPHL have similar histopathologic findings [108, 110, 111]. There is a decrease in terminal hair in favor of vellus-like hair, a decrease in anagen hairs in favor of telogen hairs, and an increase in follicular stelae (the residual fibrous tract marking where former terminal hairs resided) ending in the superficially located miniaturized follicle. A mild perifollicular lymphohistiocytic infiltrate primarily around the upper follicle is common even in those without hair loss, but is increased in extent and degree in those with pattern hair loss. Concentric perifollicular fibrosis may be present. Sebaceous glands remain intact.

10.7 Differential Diagnosis

The primary differential diagnosis for FPHL is chronic telogen effluvium (CTE). Originally described by Whiting [109], CTE is defined here as chronic diffuse scalp hair shedding of greater than 6 months' duration, often accompanied by bitemporal recession. Hair loss is usually not obvious to the evaluating physician but the hair pull is positive for telogen hairs in multiple areas of the scalp, including the occiput, as opposed to FPHL in which there should never be a positive hair pull from the occiput unless there is a superimposed telogen effluvium. The hair pull also excludes loose anagen syndrome in which multiple loose anagen hairs are generally seen and corroborated on microscopic exam. Screening by history and laboratory tests for other specific causes of hair loss are prerequisites and the diagnosis of CTE should exclude hair loss in those with known thyroid disease, connective tissue disease, obvious nutritional deficiencies or drugs known or suspected to cause hair loss. There is some thought that CTE can be definitively discriminated from FPHL by biopsy of the scalp and, indeed, there is a higher terminal/vellus hair ratio in CTE (>11:1) versus FPHL (2.2:1) [110]. However, in early FPHL, and in the elderly female patient who naturally has an increased percentage of age-related miniaturized hairs, this distinction may be difficult to make. Sinclair has noted that taking more than one scalp biopsy will increase the reliability of discriminating between FPHL and CTE [88].

Occasionally, alopecia areata can present without patches of hair loss but rather with a diffuse scalp hair loss. This hair loss is not usually limited to the top of the scalp and the hair pull is quite different from that seen in FPHL since both telogen and dystrophic anagen hairs are found in alopecia areata versus only telogen hairs in FPHL. Trichotillomania can rarely mimic FPHL since some women or girls with this psychological disorder may preferentially choose to pull out hair on the top of the scalp. However, even when the plucked hairs in the affected area have been allowed to partially regrow, the exceptionally short length of all hairs in the involved area, the normal diameter of the involved hairs and the high proportion of tapered tips of the short hairs signifying new synchronous anagen growth distinguish this

clinically from FPHL. Trichotillomania also can be definitively discriminated from FPHL by scalp biopsy.

One should also consider several cicatricial alopecias in the differential diagnosis for FPHL. In 2002, Zinkernagel and Trueb described 19 men and women with AGA that had "follicular keratosis," and perifollicular erythema and obliteration of follicles in the distribution of hair loss [114]. On biopsy, there were typical histopathological features of AGA (miniaturization, replacement of terminal hair by fibrous tracts) along with a lichenoid and an isthmus/infundibular lymphohistiocytic infiltrate and follicular loss. This condition was called "fibrosing alopecia in a pattern distribution" (FAPD). Kossard later presented another cicatricial variant of hair loss, "frontal fibrosing alopecia," occurring primarily in the same age group of Caucasian women, with the same perifollicular erythema and with the same histological findings of lichen planopilaris but with the hair loss limited to the frontal hair line [46]. Although frontal fibrosing alopecia has since been reported to occur in some cases with FAPD, clearly these conditions may occur independently and only FAPD presents any difficulties in distinguishing from FPHL.

The clinical presentation of FAPD is very similar to what Olsen has called "cicatricial pattern hair loss" or CPHL [65]. In CPHL, also seen primarily in middle-aged to older Caucasian women, there is a decrease in density on the top of the scalp in the distribution of a Ludwig pattern of FPHL plus/minus erythema but without any perifollicular papules or follicular accentuation as with FAPD (Fig. 10.9). The biopsy in CPHL is very different from FAPD and shows the typical miniaturization findings of FPHL but with an increase in fibrosis and a marked decrease in the expected number of hair follicles (normal being approximately 35 per 4-mm punch biopsy) [108, 111]. It is likely that CPHL represents an end stage of FPHL much like a Hamilton Norwood pattern VII represents an end stage of earlier patterns of MPHL. However, it is unclear why this degree of follicular drop-out should occur in only a subset of women with FPHL and how (or if) CPHL is related to FAPD.

Lastly, in the discussion of the differential diagnosis of FPHL, one must also consider central centrifugal cicatricial alopecia (CCCA), an extremely common type of permanent hair loss in African-American women [68]. The hair loss in CCCA initially presents in the central scalp, spreads centrifugally and may potentially involve all but the "Hippocratic wreath" of hair always spared in MPHL. The hair loss in well developed CCCA is accompanied by clinically obvious atrophy and baldness versus the hair loss in FPHL which never leads to baldness, even with CPHL, and does not have an atrophic scalp. FPHL may be seen in African-American women but, when present, is usually mild in degree. Whether CCCA represents the end result of severe FPHL in African-American women, perhaps related to hair care practices unique to this population [65], remains to be explored. If that is the case, it would explain the much less common occurrence of "typical" FPHL in African-American women compared to women of European descent.

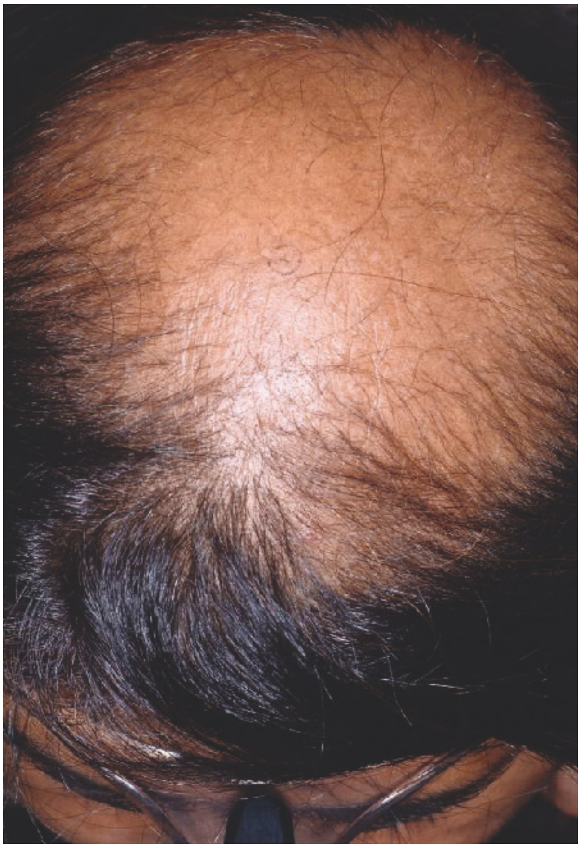


Fig. 10.9 Severe female pattern hair loss with follicular drop-out ("cicatricial pattern hair loss")

10.8 Evaluation

The primary reasons for the evaluation of women with the typical clinical picture of FPHL are to: (1) rule out close mimickers of FPHL not otherwise possible by clinical exam alone; (2) determine if there are treatable factors that may negatively impact on the therapeutic interventions for FPHL or in themselves are causing hair loss; and (3) determine the potential reversibility of the hair loss process. A recent consensus publication on this topic by experts in the field offers a complete overview of this topic [69].

A history should include the time of onset of hair loss, the location of the hair loss, whether increased shedding was present at onset and continues, and the relationship of hair loss to significant life events, illness, surgery, changes in diet or weight loss or new medications within 6 months prior to the hair loss onset. Questions should include whether the menses in the third to fourth decades were regular or required oral contraceptive agents to regulate, whether the woman was able to conceive without artificial stimulation, whether hirsutism is present and being treated and, if so, when it started and whether a family history of the same is present. It is important to know if the menses are now regular, changing or absent, and whether any supplemental hormones have been stopped or started in the recent past.

Physical exam should include the scalp with attention particularly to whether hair loss excludes the occiput, which is typical of FPHL: this can be ascertained by comparing the part width in the occiput with that on the top of the scalp [60]. Notation should be made as to any patches of hair loss, focal atrichia, broken hairs, general scalp erythema or atrophy or perifollicular erythema. Hair pull should be performed on the top, sides and occiput and the proximal ends of any hairs evaluated microscopically to ensure only telogen hairs. Signs of hirsutism should be looked for and nails should be evaluated for pits. A scalp biopsy should be done from the involved area when the diagnosis is in doubt or to determine the potential reversibility of the hair loss.

Screening blood work should always include at least a thyroid-stimulating hormone (TSH) if not also a free thyroid hormone level (T_4): any telogen effluvium related to thyroid deficiency or excess is imminently treatable and the related hair loss reversible. It is probably also wise to check the patient's iron status given that there is some question about the relationship of iron deficiency to FPHL [96] and a suggestion that the response to cyproterone acetate and ethinyl estradiol for FPHL is diminished in the face of uncorrected iron deficiency [81]. Moreover, iron deficiency anemia can be the sign of a serious underlying medical problem. To screen for iron deficiency, a serum ferritin is a reasonable test of iron stores but because it is an acute phase reactant and will be elevated in the face of acute inflammation for example, a sedimentation rate should be done along with the ferritin. If the ferritin is normal in the face of an elevated sedimentation rate, one must do additional tests [iron and total iron binding capacity (TIBC)] to confirm that iron stores are normal. A complete blood count (CBC) should be done to rule out anemia including iron deficiency anemia. Iron deficiency should be corrected with oral supplements to a ferritin level of at least 40 ng/ml, perhaps higher.

Although there are some data to support that MPHL, especially vertex hair loss, is related to coronary artery disease in men [69], the data regarding this in women with FPHL are scanty. In a study of 106 women <55 years old given an angiogram because of symptoms or tests suggestive of coronary artery disease, 29% of women with AGA versus 11% of women without AGA were noted to have angiographically diagnosed coronary disease [53].

10.9 Medical Treatment

10.9.1 Topical Minoxidil

To be effective in FPHL, a compound must: (1) stimulate a telogen to anagen transition, (2) retard the onset of catagen/telogen and/or (3) enlarge the dermal papilla/matrix in order that a thicker diameter hair is produced. Although there are many compounds that purport to do one or more of these, the only compound at the current time that has been found effective in the treatment of FPHL in multicenter controlled trials is topical minoxidil. Minoxidil is a piperidylpyrimidine derivative that causes hypertrichosis when given systemically for hypertension [67]. It causes vasodilatation through the potassium channel-opening activity of its active metabolite, minoxidil sulfate [54]. The exact mechanism of minoxidil in inducing hair growth is unclear but it does not appear to have antiandrogen effects but rather appears to increase follicular proliferation directly. Studies in both the stumptail macaque and humans confirm that topical minoxidil promotes anagen and leads to an increase in the size of effected hair follicles [54, 101].

In two similarly designed studies, one in the US and one in Europe, with a combined total of over 500 women aged 18–45 years old with Ludwig I or II FPHL, a 2% topical solution of minoxidil was shown to cause a statistically significant increase in representative target area hair counts compared to placebo (16% versus 7% and 24% versus 14% respectively) at 32 weeks [26, 44]. In another multicenter US-based trial of 381 women age 18–49 years old with FPHL, a 5% topical minoxidil solution was also found to be statistically superior to placebo with an increase of 17.3% or 24.5 hairs/cm^2 target area compared to 6.7% or 9.4 hairs/cm^2 target area respectively at the conclusion of the 48-week study [49]. Examples of increased hair growth in women with FPHL on 2% and 5% topical minoxidil solution are shown in Fig. 10.10 [49].

Topical minoxidil has been on the market since 1988 and has few side-effects. Contact dermatitis occurs in fewer than 8% of patients, slightly more frequently with

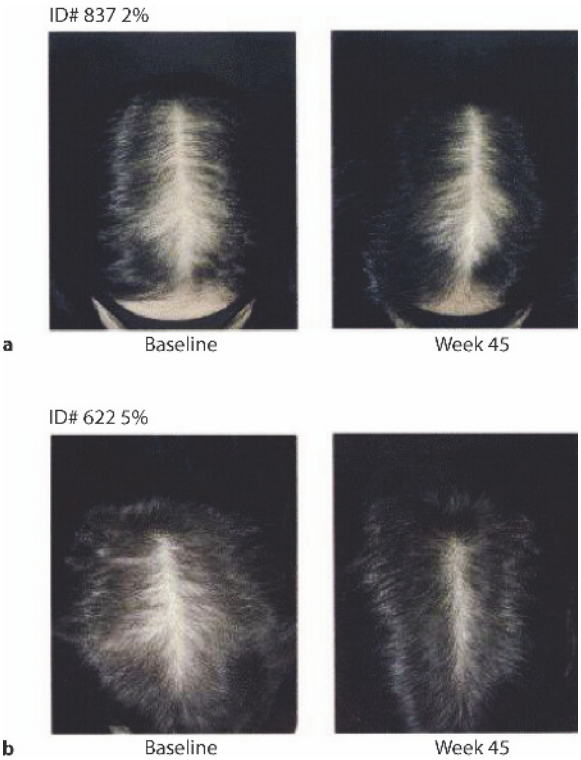


Fig. 10.10a,b Clinical photographs of patients with FPHL treated with 2% topical minoxidil solution (**a**) and 5% topical minoxidil solution (**b**). (Reprinted with permission from Lucky et al. [49])

the 5% versus 2% solution, which has a much higher concentration of propylene glycol, a frequent irritant. A new formulation of 5% topical minoxidil in a foam vehicle without propylene glycol has recently been approved in the USA [71] and may lower the incidence of this potential side-effect. Hypertrichosis occurs in 3%–5% of women using the 2% topical minoxidil solution and in a slightly higher incidence in those using 5% topical minoxidil solution [64]. The hypertrichosis in women is almost always bilaterally symmetrical growth of vellus hair over the upper cheeks and sideburn area, which suggests a systemically initiated process. However, if hypertrichosis is systemically rather than locally triggered, it must be at much lower blood levels than that responsible for other minoxidil effects: the blood levels for all 307 study subjects treated with either 2% or 5% topical minoxidil in a multicenter trial were below the level (21.7 ng/ml) known to cause pulse rate changes, the most sensitive indicator of systemic minoxidil effects [29, 49].

Because this drug is available over the counter, patients who use topical minoxidil have often not been instructed on certain practical, but critical, aspects of treatment. First, the drug must be applied to the dry scalp twice daily for at least 6 months before making a decision about efficacy. Second, because topical minoxidil stimulates a surge of anagen, there is often increased shedding of those discarded telogen hairs over the first month of use. Third, the drug does need to be used continuously to preserve any positive response but if the patient decides to stop the use of topical minoxidil, she will lose only what she has gained over a period of 3–4 months [66].

10.9.2 Antiandrogens

There are three antiandrogens that may be used in FPHL that are approved in various countries for various indications. For example, spironolactone is approved in the USA as a diuretic for the treatment of hypertension and in Australia as a treatment for hirsutism; flutamide is approved in the USA as a treatment for prostate cancer in combination with a luteinizing hormone-releasing hormone; and cyproterone acetate is unavailable in the USA but is approved in Britain as a treatment for acne and hirsutism. Each has its own advantages and disadvantages in the treatment of FPHL with multicenter controlled comparative efficacy trials lacking in this disorder. All can cause feminization of a male fetus in a pregnant woman taking the drug and thus an effective means of contraception must be in place at the time of initiating treatment with one of these drugs and for the duration of therapy.

10.9.3 Spironolactone

Spironolactone, as an antiandrogen, blocks both the production of testosterone in the adrenal gland by decreasing the activity of cytochrome P_{450}-dependent enzymes and is also a competitive inhibitor of DHT-receptor binding and nuclear translocation [20, 48]. The major metabolites are canrenone and potassium canrenone with half-lives of about 20 h and which are eliminated via the biliary route [86, 95].

The minimally effective dose of spironolactone appears to be 100 mg per day, a dosage based more on the treatment of hirsutism than alopecia, with the usual doses given being 100–200 mg per day. There are no studies to address a dose effect in FPHL and published results of >100 mg per day are primarily on cohorts of fewer than ten women [10, 82]. However, there is one 12-month trial of spironolactone 200 mg per day in 40 women with FPHL with documented efficacy in 45% of women [89]. Despite a lack of further documentation of efficacy, spironolactone is used regularly in the

treatment of women with FPHL, particularly in those women with documented hyperandrogenism.

Hyperkalemia ia a potential side-effects of spironolactone related to its aldosterone antagonist/potassium-sparing effect on the kidney, and potassium levels should be checked after starting the drug. Since spironolactone may cause breast tenderness, irregular menses and mood swings,it is wise to put women of child-bearing potential on an oral contraceptive agent prior to beginning spironolactone. There is one oral contraceptive agent, Yasmin®, whose 3 mg of progesterone (drospirenone) has an inherent spironolactone-like effect equivalent to 25 mg of spironolactone, not enough by itself to expect to see an effect on FPHL [112].

10.9.4 Flutamide

Flutamide, or its metabolite 2-hydroxy-flutamide, is a non-steroidal pure antiandrogen with no intrinsic androgenic activity. It inhibits the binding of testosterone to the androgen receptor, the negative feedback of gonadal steroids at the hypothalamic–pituitary level, and adrenal 17,20-desmolase, with a resulting decrease in DHEA and DHEAS [22, 86]. Excretion is primarily renal [94].

Flutamide has been evaluated only in women with hair loss who also have hyperandrogenism. Carmina and Lobo evaluated 250 mg of flutamide daily versus cyproterone acetate versus finasteride versus observation alone in 48 women (12 women in each group) with FPHL and documented hyperandrogenism [14]. The flutamide group had a statistically significant improvement in the Ludwig score and in the investigator assessment over the observation group. Extrapolation from anecdotal reports in women with hirsutism who also had hair loss showed that 250 mg of flutamide twice daily in combination with an oral contraceptive agent had cosmetically acceptable growth in six out of seven women and may have efficacy in alopecia beyond that of spironolactone [23]. Its primary side-effects are gastrointestinal including diarrhea although the use of flutamide is limited by its known hepatotoxicity, which can be fatal [34].

10.9.5 Cyproterone Acetate

Cyproterone acetate blocks DHT-androgen receptor binding and, given its steroid structure, has progestogen and antigonadotropic properties [40]. In women of child-bearing potential, estrogens are usually given with cyproterone acetate to reinforce the latter effect and to ensure regular menses. Two combinations of cyproterone acetate with 50 µg ethinyl estradiol are utilized for their antiandrogen effect in premenopausal women: (1) 100 mg along with estrogen on days 5–15 and estrogen alone on days 16–25 (cyclical antiandrogen therapy or CAT) for hirsutism or (2) 2 mg in combination with estrogen on days 5–25 (Diane®). In postmenopausal women, 50 mg of cyproterone acetate daily may be used alone. Potential side-effects are dose related and include menstrual irregularity, weight gain, breast tenderness, decreased libido, depression, and nausea [103].

There have been few controlled clinical trials of cyproterone acetate in FPHL. In one study 20 female patients with AGA were treated for 1 year with daily 50 µg ethinyl estradiol and 2 mg cyproterone acetate (Diane®) plus an additional 20 mg cyproterone acetate on days 5–20 of the menses and were compared to 10 untreated control patients with AGA for 1 year [76]. Trichogram results as well as hair diameter on the fronto-cranial and temporal scalp were assessed. There was a statistically significant increase in the anagen/telogen ratio but no decrease in vellus hairs on the fronto-cranial scalp in the cyproterone acetate group compared to controls. In another study, 40 patients with FPHL were treated with cyproterone acetate for 12 months, 22 postmenopausal women with 50 mg cyproterone acetate daily, and 18 premenopausal women with 100 mg cyproterone acetate daily for 10 days each month along with a combination oral contraceptive pill [89]. Of 40 women, 17 (42.5%) had a positive response documented photographically. These results were almost identical to the comparative group of 40 patients treated with spironolactone. A 48-week trial conducted by Vexiau et al. included equal numbers of women (33 each group) with female AGA treated with 52 mg per day of cyproterone acetate plus ethinyl estradiol 35 µg for 20 of every 28 days or 2% topical minoxidil solution 1 ml bid plus combined oral contraceptive use [105]. Between baseline and 12 months, there was no significant difference in the mean number of target area hairs in the cyproterone group but an increase in the minoxidil group. There was no difference in the results with cyproterone acetate and FPHL with the presence or absence of other signs of hirsutism. Dawber et al. has suggested that there is a minimally effective dose of cyproterone acetate, as 24 out of 29 women had improvement in FPHL when treated with 50 µg ethinyl estradiol and 200 mg cyproterone acetate daily but 14 of 17 who remained on Diane® (2 mg cyproterone acetate) failed to maintain that response [24].

Mortimer et al. reported a positive response to treatment with CAT in three women with FPHL [55]. Hammerstein treated patients with hirsutism and various other potentially androgen-related effects with cyproterone acetate, and although the hirsutism, acne, and seborrhea responded to the drug, the AGA did not [40]. Similarly, Ekoe found that 6 out of 11 patients with hair loss and hirsutism treated with cyproterone acetate 100

mg on days 5–14 and ethinyl estradiol on days 5–25 did not even have stabilization of hair loss [28].

10.9.6 Other Antiandrogens

Cimetidine is an H2 antihistamine that inhibits DHT binding. One uncontrolled study of 300 mg five times a day suggests some efficacy in FPHL [2].

10.9.7 5α-Reductase Inhibitors

As previously noted, in a large controlled multicenter trial of postmenopausal women with FPHL, the results with finasteride 1 mg were not found to be significantly different from placebo at the end of one year [77]. However, there were individual subjects in this trial who did have hair growth on finasteride 1 mg and there have since been anecdotal reports of finasteride being effective in postmenopausal women without hyperandrogenism at 1 or 2.5 mg doses [92, 97, 102] and in women with hyperandrogenism at 2.5 mg [87]. There are no placebo or active controlled studies of finasteride in premenopausal women with early-onset FPHL but there is now a controlled open label study of 37 premenopausal women with FPHL and no hyperandrogenemia or signs of hyperandrogenism [42]. These women were given 2.5 mg of finasteride daily in conjunction with the oral contraceptive Yasmin®. Efficacy was judged based on global photographs and the deLachariere hair part density scale. At the conclusion of 12 study months, 60% of the women had increased hair growth as documented by global photographs (11 of 37 moderate or greater hair growth) and 12 of 37 (32%) had an increase in hair density. There were no adverse reactions. Camacho has reported the effectiveness of finasteride 2.5 mg in 41 women with FPHL and SAHA (seborrhea, acne, hirsutism, and acne) [11].

Finasteride, a type II 5α-reductase inhibitor, has been shown in men to decrease serum DHT by 67% [80] with 1 mg and 68.5% with 5 mg [27] and scalp DHT by 64.1% with 1 mg and 69% with 5 mg [27]. Based on the lack of a significant difference in DHT suppression between 1 and 5 mg of finasteride, there would appear to be no advantage to taking 1 versus 2.5 mg per day of finasteride as has been done in some reports of women with FPHL. Dutasteride is a dual type I and type II 5α-reductase inhibitor currently approved in a 0.5-mg dose form for prostatic hyperplasia. In a comparative study of men with MPHL, serum DHT was suppressed by 92% versus 73% and scalp DHT by 51% versus 41% in men treated with 0.5 mg dutasteride versus 5 mg finasteride respectively [70]. Suppression of DHT was correlated with hair count in men with MPHL. Dutasteride has a much longer half-life than finasteride (4 weeks versus 6–8 hours) with prolonged suppression of DHT and has not been subjected to any clinical trials in women. However, Olszewska reported on one postmenopausal woman with FPHL who responded to dutasteride and not finasteride [72]. Women of child-bearing potential should be on an effective form of contraception prior to beginning any 5α-reductase inhibitor since 5α-reductase inhibitors have the potential to cause feminization of a male fetus: an oral contraceptive pill is the contraceptive of choice for the additional reason that it will decrease production of circulating androgens. Given its longer half-life, dutasteride should not be taken by women of child-bearing potential.

10.9.8 Estrogens

Estrogens given systemically increase the production of SHBG leading to a decrease in free testosterone. Topical 0.025% 17α-estradiol preparation appeared to stabilize hair loss when applied for 6 months by seven women with AGA and/or increased telogen hair shedding compared to two female controls [73]. Interestingly, hair loss has not been one of the common side-effects reported with systemic aromatase inhibitors [90].

10.9.9 Estrogen Receptor Antagonist

Largely based on the anagen-promoting activity of an ER antagonist in mice [58], a proof of concept study was done in 70 postmenopausal women with Ludwig I or II FPHL treated with either fulvostatin (an estrogen receptor antagonist) or placebo for 16 weeks [33]. There was no statistically significant difference between groups in hair density, cumulative hair thickness or growth rate. In clinical practice, hair loss or growth has not been a common side-effect of estrogen receptor inhibitors [35].

10.9.10 Melatonin

Melatonin has been shown to promote anagen induction in animals. In a double-blind randomized placebo-controlled study, women aged 20–70 with diffuse alopecia (n= 28) or AGA (n= 12) were treated with 1 ml daily of 0.1% melatonin–alcohol solution versus vehicle topically for 6 months. Efficacy was determined by trichograms in the frontal and occipital areas [30]. At the conclusion of the study of women with FPHL, there was a statistically significant increase from baseline in anagen hairs in the occiput in the topical melatonin group (mean 76.3 to 85.2 hairs) compared to placebo (mean 78 to 82 hairs) but no difference from placebo in the frontal area.

10.10 Surgical Treatment

Hair transplants may be extremely useful in FPHL, the limitations being adequate donor hair, reasonable expectations, and cost. Before the development of follicular unit transplanting and slit grafting, donor tissue was removed by round trephines and the grafts were placed into holes made by marginally smaller trephines. Since the recipient site in FPHL was not bald but only less dense than normal, this led to the unnecessary removal of some viable terminal hair when preparing the recipient hole. The advent of follicular unit transplants, in which 1- to 2-unit grafts are placed into the recipient area by a hypodermic needle hole or slit made by a scalpel, has eliminated this. Grafts are generated from elliptical donor strip harvesting the same in women as in men, except that the donor area may be more restricted in women than men: the temporal and inferior parietal/occipital areas are not used for donor areas in women in order to prevent future limitations in hair styles [100]. In the focal atrichia areas, Unger either places larger follicular units or removes the bald skin by trephine and places a larger graft into these new recipient sites. Realistic goals for transplant should established: an increase in hair density in strategic areas seems feasible in most women with further goals dependent on the donor site and number of sessions. Postoperatively, there may be a temporary loss of hair in both the donor and recipient areas. This effect may be mitigated by the use of topical minoxidil [4].

Summary for the Clinician

Female pattern hair loss is a common condition with two primary ages of onset: early, which overlaps with male pattern hair loss (MPHL), and late, which presents in the early fifth decade and overlaps with menopause. Most patients with FPHL do not have documented signs of hyperandrogenism or hyperandrogenemia. The response to antiandrogens and 5α-reductase inhibitors highlight the issues surrounding the etiology of FPHL, which is still unclear for all patients. Finasteride, a 5α-reductase inhibitor, was shown not to be effective in a placebo-controlled trial in postmenopausal women with FPHL but there is encouraging information about its efficacy in early-onset FPHL and information from non-placebo-controlled studies that it may be useful in some postmenopausal women as well. Topical minoxidil remains a mainstay of treatment and hair transplants now offer a viable alternative effective treatment for many women with FPHL.

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Chapter 11

Primary Cicatricial Alopecia

Elizabeth Katrina Ross, Jerry Shapiro

11

Synonyms
Primary scarring alopecia

Key Features

- Group of largely uncommon disorders.
- Result from primary destruction of the hair follicle, often affecting the scalp.
- Cause and pathogenesis incompletely understood.
- Clinical hallmark loss of follicular ostia.
- Classified provisionally by primary inflammatory cell infiltrate.
- Prompt intervention key to thwarting continued hair loss.
- In general, formal, controlled studies on treatment are lacking.

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11

The primary cicatricial alopecias are a largely uncommon group of disorders characterized by permanent destruction of the hair follicle – often involving the scalp alone – with relative sparing of the nonfollicular structures in the skin. Hallmark features are absent follicular ostia on exam and scarred fibrous tracts that mark extinct follicles on pathology.

Although several types of primary cicatricial alopecia have been recognized since the nineteenth century, little is known about the cause and pathogenesis of individual disease. All presumably result from irreversible injury to the stem-cell-rich bulge area, which is required for cyclic regeneration of the lower follicle [115]. Indeed, in all forms of primary cicatricial alopecia this portion of the follicle is generally affected. In contrast, when the lower, nonpermanent portion of the follicle is involved, as in alopecia areata, these critical cells are left unperturbed and the potential to regrow hair remains intact.

Known aspects of evolving disease in humans and rodent models of primary cicatricial alopecia (for which there is no human correlate) suggest that primary follicular destruction can result from a variety of means, including: (1) sebaceous gland pathology, (2) outer root sheath compromise, and possibly even (3) primary follicular stem cell failure [88, 145, 162]. In some conditions, a genetic propensity (e.g., in keratosis follicularis spinulosa decalvans) and exogenous triggers (e.g., ultraviolet light in discoid lupus erythematosus, medications in lichen planopilaris and acne keloidalis, and possibly *Staphylococcus aureus* in folliculitis decalvans) are pathoge-

netic factors. Now in the early twenty-first century, a concerted effort between bench researchers, clinicians, and pathologists is needed to further our understanding about this diverse, intriguing group of conditions.

11.1 Approach to the Patient with Cicatricial Alopecia

Prompt diagnosis and treatment of active disease to halt further hair loss is the goal. Clinical diagnosis of primary cicatricial alopecia should be confirmed by histopathology. A single 4-mm punch biopsy sample is recommended, taking care to choose a biopsy site with clinically representative active disease which is usually at the advancing, hair-bearing edge of an area of alopecia. Symptoms, inflammatory stigmata, and a positive pull test are helpful signs. Transverse sectioning of the biopsy specimen is conventionally advocated to ensure that all follicles are assessed at multiple planes; however, loss of critical diagnostic features in the epidermis, superficial dermis, and panniculus with this mode can impair interpretation [49, 69]. Obtaining a second specimen for vertical sectioning can improve diagnostic yield, but may still not allow distinction among predominantly lymphocytic or neutrophilic inflammation [48, 111]. The authors use this dual approach when faced with clinically puzzling cases and when discoid lupus erythematosus is considered. The specimen to be sectioned vertically is bisected, with half sent for hematoxylin-eosin staining and the other for direct immunofluorescence. Elastin stains can be used in more advanced disease to help distinguish between the more common lymphocytic predominant disorders (which often overlap both clinically and histopathologically) based on different patterns of scar formation [47].

Once the diagnosis is established, active disease must be treated immediately to thwart further hair loss. Although hampered in large part by the lack of formal, controlled studies, there are ample empiric data in most conditions to devise a tiered treatment plan. Flexibility is key. In some, the hair loss continues despite these measures, and cosmetic aids and supportive care are what are needed most.

Table 11.1 Working classification of primary cicatricial alopecias based on predominant inflammatory cell involved [a]

Lymphocytic	**Lichen planopilaris**
	– **Sparse, curly, and fair hair**
	– **Classic variant**
	– **Frontal fibrosing alopecia**
	– **Piccardi–Lassueur–Graham Little syndrome**
	– **Fibrosing alopecia in a pattern distribution**
	Pseudopelade of Brocq
	Central centrifugal cicatricial alopecia
	Alopecia mucinosa
	Keratosis pilaris spinulosa decalvans/ Folliculitis spinulosa decalvans
	Discoid lupus erythematosus
Neutrophilic	**Folliculitis decalvans**
	Perifolliculitis capitis abscedens et suffodiens
Mixed	**Acne keloidalis**
	Acne necrotica
	Erosive pustular dermatosis of the scalp

[a] Revised from NAHRS classification scheme, *J Am Acad Dermatol* 2003;48:103-10 [123]. Entities in *italics* may not be appropriately classified, distinct, or clearly primary in nature. See text for details.

11.2 Classification

A standardized classification scheme was adopted by the North American Hair Research Society in 2001 as a fulcrum for further discussion, debate, and research [123]. It is based on the primary inflammatory cell involved in active disease (lymphocytic, neutrophilic, or mixed) (Table 11.1). Modification is expected as advances occur. The chapter will address the entities listed in Table 11.1 in the order in which they appear.

11.3 Lymphocytic Disorders

11.3.1 Lichen Planopilaris

Lichen planopilaris is a follicular form of lichen planus. Three clinical variants result in cicatricial alopecia: (1) classic lichen planopilaris; (2) frontal fibrosing alopecia; and (3) Piccardi-Lassueur-Graham Little syndrome.

11.3.1.1 Classic Lichen Planopilaris

Synonyms
follicular lichen planus

Key Features

- Adults of all races affected, with female predominance.
- Intensely pruritic.
- White to ivory colored, depressed, reticulate or polygonal-shaped alopecic plaques with perifollicular hyperkeratosis and variable erythema at the hair-bearing margin.
- Positive pull test for anagen hairs when active.
- Lichen planus exists elsewhere in some.
- On histopathology, lichenoid interface dermatitis of the upper follicle associated with vacuolar change, apoptotic keratinocytes, hyperkeratosis, and hypergranulosis.

11.3.1.1.1 History

In 1895, Pringle presented a case of lichen planus associated with "lichen pilaris" of the neck, later commenting on other cases of folliculocentric lichen planus, some of which were associated with patchy alopecia of the scalp [139].

11.3.1.1.2 Epidemiology

Classic lichen planopilaris is largely seen in adults, about twice as often in females based on most reports [34, 112, 166, 176]. Onset usually occurs between the ages of 25 and 70 years, typically in the mid-40s to early 50s. Children are less commonly affected. All races are susceptible.

11.3.1.1.3 Pathogenesis

Lichen planopilaris is a T-cell disorder that involves the upper follicle, with an increased CD8:CD4 ratio and a marked diminishment of Ki-67-staining proliferative cells in the bulge, compared to normal follicles [112]. Certain drugs are known to trigger disease (e.g., gold and quinacrine hydrochloride), but in most cases the cause is unknown [145].

11.3.1.1.4 Clinical Features

Intense pruritus and increased hair shedding are common presenting complaints [34, 110, 145]. Pain, burning, and scalp tenderness may also be experienced. The central scalp is a common target. Characteristically, perifollicular hyperkeratosis with variable erythema is seen at the hair-bearing margin of ivory-white atrophic reticulate or polygonal alopecic plaques (Fig. 11.1a,b). Features of nonfollicular lichen planus are usually absent. In early disease, little to no associated alopecia may be found. A positive pull test for anagen hairs at sites of

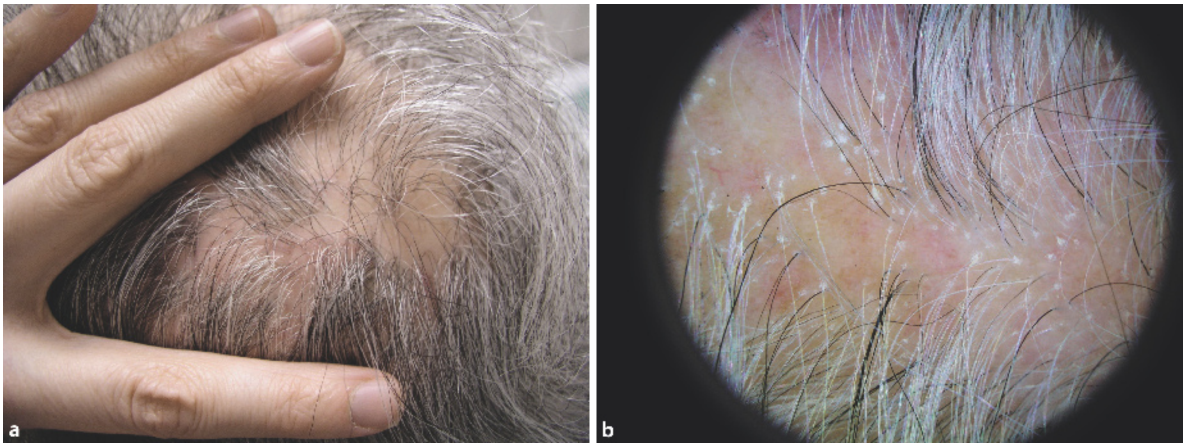


Fig. 11.1a–e Classic lichen planopilaris. **a** Perifollicular scale and erythema at the margin of scarred alopecic areas. **b** Dermoscopy at 16× magnification showing perifollicular scale

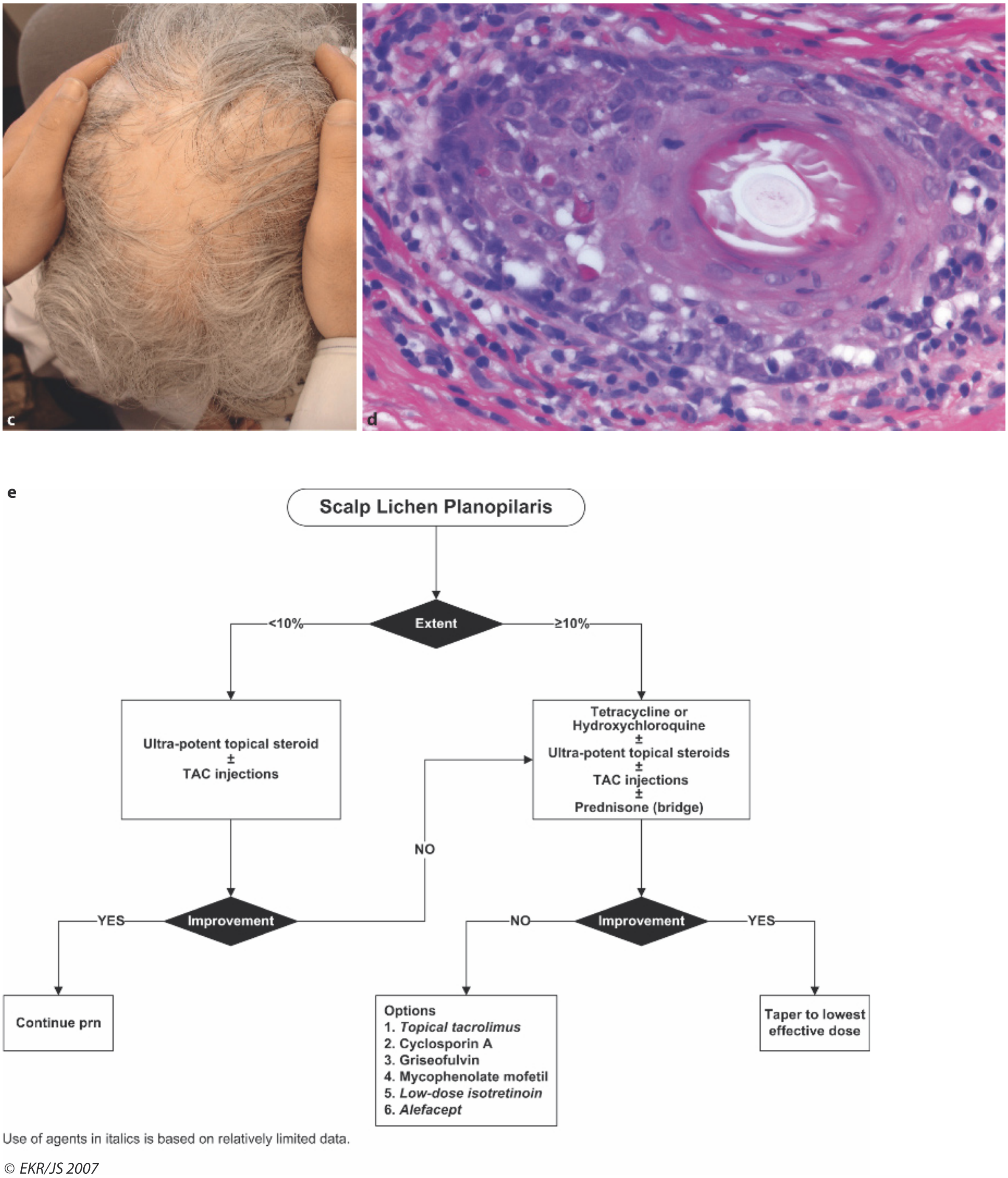


Fig. 11.1a–e *(continued)* **c** Overview showing extensive central scarring. **d** Histopathology at 40× magnification showing peri-infundibular lichenoid interface changes. **e** Treatment algorithm

perifollicular inflammation may be the only indicator of active disease. The hair loss that follows can be limited or extensive (Fig. 11.1c). Remaining interspersed hairs can impart remarkable camouflage in some. Uncommonly, near-complete hair loss can develop. In general, the course of disease is indolent, with episodic bursts of activity.

Nonscalp lichen planus develops in 50% of individuals, often after the onset of scalp disease, according to one study [110]. When the form is lichen planopilaris or bullous, fulminant scalp disease may be seen [145]. Androgenetic alopecia frequently coexists (28%) [166].

An ulcerative variant of scalp lichen planopilaris occurs rarely; although linked to hepatitis C in one case the significance of this association is unknown [24].

11.3.1.1.5 Pathology

In early disease, a lymphocytic lichenoid interface dermatitis is seen to affect the infundibulum and isthmus, in association with vacuolar alteration, scattered dyskeratotic and necrotic keratinocytes in the basal layer, and colloid bodies in the adventitial dermis [5, 110, 112, 156] (Fig. 11.1d). This is accompanied by infundibular hyperkeratosis and hypergranulosis and atrophic or absent sebaceous glands. The adjacent epidermis may show features of typical lichen planus. With progression, the lichenoid infiltrate is displaced peripherally by lamellar fibroplasia that is seen to surround an atrophic, "squamatized" follicular epithelium. Follicular destruction follows, marked initially by foreign-body hair shaft granulomas, and then by longitudinal fibrotic tracts at the sites of extinct follicles – hallmark features seen in most of the primary cicatricial alopecias. Direct immunofluorescence, when positive, usually shows patchy deposition of fibrinogen and globular IgM along the follicular basement membrane zone. IgA is seen less commonly. In advanced disease, the elastin staining pattern reveals a superficial wedge-shaped scar associated with loss of the upper follicular elastic sheath [47].

11.3.1.1.6 Differential Diagnosis

In its characteristic form, classic lichen planopilaris is distinctive. Problems differentiating lichen planopilaris from other entities arise when the condition is subacute or burnt out, in which case it most closely resembles pseudopelade of Brocq. Distinction between these two entities can be difficult and fuels the debate about their interrelationship, as will be discussed in Sect. 11.3.5.1.

11.3.1.1.7 General Treatment Measures

Management of active primary cicatricial alopecia depends on several variables including diagnosis, age, symptom severity, extent, and patient preference. In general, local disease (<10% scalp surface area) is treated with topical therapy (choice of gel, foam or other vehicle based on patient choice and hair shaft type) and/or lesional injections of triamcinolone acetonide (typically used in doses of 3 to 10 mg/ml, which the authors disperse in 0.1-ml aliquots at 1-cm intervals using a 0.5-in 30-gauge needle, with a maximum dose of 20 mg per monthly session). Treatment is usually directed to active hair-bearing sites with the exception of discoid lupus and perifolliculitis abscedens et suffodiens, two conditions in which hair regrowth in alopecic sites is possible if the problem is caught early. Because formal studies on treatment efficacy are lacking for most conditions, where appropriate the authors suggest that half-head/lesion application be done for 2–4 weeks to determine true effect. Rapidly advancing disease, disease refractory to topical treatment, and more widespread scalp involvement usually require systemic measures.

11.3.1.1.8 Treatment of Classic Lichen Planopilaris

Treatment of classic lichen planopilaris is shown in Fig. 11.1e and Table 11.2.

Possible offending drugs should be eliminated or substituted with an agent from another class, if possible. First-line therapy for localized disease is a topical mid- to ultra-potent corticosteroid, which can induce complete or partial remission in around two-thirds [34, 145]. The authors typically use clobetasol propionate lotion or foam. Continued use may be required to maintain the effect. Monthly intralesional injections of triamcinolone acetonide can be added to improve outcome in partial responders. Alternatively, combination therapy may be started outright, particularly in those with highly active, symptomatic disease. Second-line options include topi-

Table 11.2 Evidence-based ratings of treatments for classic lichen planopilaris

Topical agents	
Corticosteroids	2
Tacrolimus	5
Ciclosporin	5
Intralesional triamcinolone	4
Systemic agents	
Prednisone	4
Tetracycline	4
Hydroxychloroquine	4
Retinoids	5
Cyclosporine	4
Griseofulvin	4
Mycophenolate mofetil	4
Alefacept	5

11

cal tacrolimus and ciclosporin. The authors have used twice-daily topical tacrolimus (0.1%) in an ointment or lotion base (depending on hair type) with variable benefit in some within a few weeks of starting therapy, ranging from symptomatic relief to a few months of disease-free activity. The ointment base of tacrolimus can be difficult to remove with shampooing – a real problem in those with straight, fine, Caucasoid hair; compounded lotion-based formulations are best used in these individuals. Because of the theoretical risk of treatment-related carcinoma, currently under discussion, chronic use should be avoided when possible. Successful treatment with topical ciclosporin (unknown concentration, twice daily for 20 days, followed by daily use for 40 days) in one topical steroid-refractory case has also been reported [34].

In those who require systemic therapy, a short course of prednisone (0.5–1 mg/kg per day for 4–8 weeks) can be instituted to slow and even halt rapid hair loss, or as a bridge while waiting for another agent to take effect (e.g., hydroxychloroquine) [145]. Alternatives of variable benefit include tetracyclin (1g/day) hydroxychloroquine (typically 200 mg twice daily), isotretinoin (used at acne doses, but trial of low-dose treatment recommended initially), ciclosporin (3–5 mg/kg per day for 3–5 months), griseofulvin (250 mg twice daily for 7–10 months), and mycophenolate mofetil (started at 500 mg twice daily for 1–2 months, and increased to 1 g twice daily if needed for 6 months at which time remission should occur) [137, 172, 181]. Small case reports suggest low-dose tretinoin (10 mg daily for 1–10.5 months) and alefacept (15 mg/week IM for 12 weeks) may also be effective [56, 145]. Thalidomide and low-dose heparin are largely ineffective [78, 145]. Ultimately, no single reliably effective drug has yet emerged for treatment of classic lichen planopilaris.

11.3.2 Frontal Fibrosing Alopecia

Synonyms
postmenopausal frontal fibrosing alopecia

Key Features

- Largely affects postmenopausal women.
- Symmetric band of frontotemporal recession often associated with eyebrow loss.
- Histology and immunofluorescence resemble lichen planopilaris.

11.3.2.1 History

This relatively new entity was first recognized by Kossard in 1994 who reported six cases of progressive band-like frontotemporal recession in postmenopausal women [87]. Histology and immunofluorescence resembled lichen planopilaris. Effective treatment was elusive.

11.3.2.2 Epidemiology

Most affected women are postmenopausal, between the age of 40 and 80 years [87, 90, 114, 170, 173]. Onset in "premenopausal" women in their 30s and 40s, and, rarely, in men has also been reported [86, 90, 114]. Published cases originate from Australia, Europe, Canada, the United States, and Korea.

11.3.2.3 Pathogenesis

Frontal fibrosing alopecia has been classified as a form of lichen planopilaris based on similar histopathology, and the coexistence of classic scalp lichen planopilaris or lichen planus elsewhere on the body in some subjects [87, 90]. One recent study showed that vellus-like and intermediate follicles are more selectively affected, as seen in "fibrosing alopecia in a pattern distribution" – a patterned lichen planopilaris or lichenoid tissue reaction in areas of androgenetic alopecia, which can present with features similar to those of frontal fibrosing alopecia (see 11.3.4) [170, 180]. While frontal fibrosing alopecia often develops in women with androgenetic alopecia, its onset it also not uncommon at an age well past that accepted for the condition. Even more intriguing is the finding that both conditions appear to respond to treatment with antiandrogen therapy and topical minoxidil [114, 170, 180]. This suggests a hormonal basis for the disease that may or may not be shared. In frontal fibrosing alopecia, the lack of any correlation to peripheral sex hormone levels or the use of hormone supplementation has led to the view that regional factors are involved. These factors appear to be inherent to the aging frontotemporal scalp rather than to the hair follicle itself, as evidenced by the occurrence of disease precipitated by transplantation of occipital terminal hairs to affected androgenetic frontal scalp in an elderly man [86].

11.3.2.4 Clinical Features

Frontal fibrosing alopecia is marked by a band of symmetric alopecia along the frontal and frontotemporal



Fig. 11.2 Frontal fibrosing alopecia. Symmetric band-like recession of the frontotemporal hairline associated with lateral eyebrow thinning

hairline [90, 114, 170, 173] (Fig. 11.2). Symptoms are usually absent, but may include mild itch. The depth of recession can range from 0.5 to 8 cm, within which may be contained a few remaining hairs. The affected, bare skin is atrophic, smooth, shiny, and often lighter than the chronically sun-exposed forehead skin, which permits one to surmise where the frontal hairline originated. Loss of follicular ostia can be hard to appreciate. In the immediate hair-bearing periphery, within about 1–2 cm, perifollicular erythema and/or mild hyperkeratosis may be seen. The pull test is usually negative. Variants include those with midline frontal hairline loss (authors' observation) and alopecia that wraps around the entire marginal scalp [88, 135]. Lateral or complete eyebrow loss, sometimes with perifollicular and interfollicular (authors' observation) erythema, is another common feature (Fig. 11.2). Thinning of axillary, pubic, extremity and truncal hair, sometimes associated with follicular keratosis and/or erythema, can also occur [90, 145, 170]. Classic lichen planopilaris in other scalp areas and lichen planus elsewhere on the body may coexist [145]. Androgenetic alopecia is a common second diagnosis.

Frontal fibrosing alopecia is generally slow in progression, but rapid loss has also been described [90, 114, 170]. Hair loss eventually stops after several years.

11.3.2.5 Pathology

Direct immunofluorescence, and immunohistochemical studies resemble classic lichen planopilaris, but vellus-like and intermediate hairs appear to be more commonly affected than terminal hairs. In addition, the epidermis is consistently spared [90, 135, 170].

11.3.2.6 Differential Diagnosis

Frontal fibrosing alopecia is easily confused with ophiasis. The finding of follicular inflammation at the marginal edge of the alopecia or in the eyebrows is a differentiating feature, seen only in frontal fibrosing alopecia. Frontotemporal androgenetic alopecia, another consideration, lacks the associated inflammatory changes at the hair-bearing edge and is, in general, less band like in pattern. Differentiation from traction alopecia can usually be gleaned from the history, supported by the finding of broken hairs of various lengths in the affected area.

11.3.2.7 Treatment

There is no proven effective treatment for this condition. A host of topical (e.g., corticosteroids, retinoids) and systemic (e.g., isotretinoin, acitretin, griseofulvin, and hydroxychloroquine) medications have been tried with disappointing results [145]. Recommended first-line therapy is lesional triamcinolone injections {2.5–10 mg/ml every 4–6 weeks (authors' experience) or 20 mg/ml every 3 months [114]}; this can help to slow the hair loss, although not reliably. Differences in individual response may relate to stage of disease at the time of treatment. Atrophy may be aggravated by this approach. A short course of oral prednisone (0.5–1 mg/kg per day for 1–3 months) or chloroquine (150 mg/day for 3–9 months) may be tried in nonresponders [145].

Recently two groups showed that combination oral finasteride (2.5 mg/day) and topical minoxidil (2%–5% twice daily) can arrest hair loss in some women, after 1–2 years of use [114, 170]. The lengthy treatment duration before an effect is seen could reflect the time it takes to get peak benefit from finasteride, as proven in males with androgenetic alopecia, or may reflect the natural course of disease. Addition of lesional triamcinolone injections can further improve response [114]. Importantly, side-effects of long-term use of finasteride

in women, in whom this agent is currently contraindicated, are unknown.

11.3.3 Piccardi–Lassueur–Graham Little Syndrome

Synonyms
Graham Little and Lassueur-Graham Little syndrome

Key Features

- Adult onset.
- Triad of patchy scarring scalp hair loss, nonscarring alopecia of axillae and pubic area, and follicular keratosis of the trunk and extremities.
- Histopathology debated: resembles classic lichen planopilaris or keratosis pilaris atrophicans.

11.3.3.1 History

In 1914, Piccardi reported the first case of this condition [129]. Graham Little subsequently described the features of two additional cases, one of which was referred to him by Lassueur, and became convinced that it was a form of lichen planus [66, 67].

11.3.3.2 Epidemiology

This is an uncommon condition of adults.

11.3.3.3 Pathogenesis

Piccardi–Lassueur–Graham Little syndrome is classically considered a type of lichen planopilaris; however, some consider it a distinct entity, and others a variant of keratosis pilaris atrophicans [92, 145]. There is a single case report of hepatitis B vaccine-associated disease [9], but in general, the cause of disease is unknown.

11.3.3.4 Clinical Features

Piccardi–Lassueur–Graham Little syndrome is marked by a triad of patchy scarring hair loss of the scalp, nonscarring alopecia of the axillae and pubic area, and grouped or disseminated follicular papules with spinous scale on the trunk and extremities [145]. Pruritus is variably present. Active scalp disease resembles classic lichen planopilaris in some, whereas in others erythematous, scaly, patchy alopecia is seen. Scalp involvement usually precedes the follicular eruption elsewhere by months to years, but both features can arise simultaneously. Progression of hair loss is slow and relentless in some and rapid in others. Infrequently, the face and eyebrows are also involved.

11.3.3.5 Pathology

Resemblance to both classic lichen planopilaris and keratosis pilaris atrophicans has been noted [145].

11.3.3.6 Differential Diagnosis

Clinical overlap with keratosis follicularis spinulosa decalvans underlies the debate on their relationship to one another. Unlike Piccardi–Lassueur–Graham Little syndrome, however, keratosis follicularis spinulosa decalvans is often familial, with onset of disease in childhood, variably associated with photophobia and focal palmoplantar keratoderma.

11.3.3.7 Treatment

Based on limited, anecdotal reports, successful control of disease is possible with high-potency topical corticosteroids, alone or in combination with intralesional injections of triamcinolone acetonide (10 mg/ml), and with systemic corticosteroids and ciclosporin (4 mg/kg per day for 3 months); in one case, psoralen and ultraviolet light A (PUVA) was ineffective [145]. Truncal and extremity follicular keratosis may respond to topical tretinoin [92].

11.3.4 Fibrosing Alopecia in a Pattern Distribution

In 2000, this newest form of primary cicatricial alopecia was described by Zinkernagel and Trueb who detailed their clinicopathologic findings in 19 patients [15:4, F:M; age range 35–74 years (mean age = 59)] [180]. The condition is believed to be a form of lichen planopilaris or a lichenoid tissue reaction that selectively involves miniaturizing follicles in areas of androgenetic alopecia. Lab tests for androgens are normal. The inciting cause is unknown.

Patients with androgenetic alopecia present with acute worsening of their hair loss, sometimes associated with itch or pain. Clinical exam reveals diffuse, nonpatchy cicatricial alopecia limited to the area of androgenetic hair loss. Perifollicular erythema is universally seen, often with follicular keratosis. The centrovertical scalp is typically affected, but some have frontotemporal loss similar to that seen in frontal fibrosing alopecia. Nonscalp lichen planus is absent. Histopathology reveals features consistent with a lichenoid tissue reaction that affects the upper follicle of vellus-like hairs; the adjacent epidermis is spared. Direct immunofluorescence is usually negative, but can show mild granular deposition of IgA, IgG, and IgM.

It appears that an arrest of hair loss is possible with oral antiandrogen therapy (e.g., substitution of 1 mg cyproterone acetate for norethindrone in two women on hormone replacement therapy; 10 mg cyproterone acetate alone in another women; and 1 mg finasteride in a man) combined with topical 5% minoxidil and clobetasol propionate; however, this is less than an optimal sample size. Moderate- to high-potency topical corticosteroids can provide symptomatic relief, but do not impact the hair loss. Topical tretinoin and antimalarials appear to be ineffective.

11.3.5 Pseudopelade of Brocq

Synonyms
pseudopelade

Key Features

- Majority affected are adults.
- Asymptomatic and clinically noninflammatory.
- Morphologies include multifocal lentil-sized plaques, and larger alopecia-areata-like, polycyclic or irregularly contoured larger plaques, alone or in combination.
- Positive pull test may be only indication of active disease.
- No pathognomonic features on histology; typified by lymphocytic perifollicular infiltrate around the infundibulum *without* interface change, and prominent concentric lamellar fibroplasia in established disease.

11.3.5.1 History

Neumann first described the condition in 1869, appreciating then its gross resemblance to patchy alopecia areata [20, 118]. In 1888, Brocq named the condition *pseudo*pelade – "pelade" being the French term for alopecia areata – and went on to systematically characterize its clinical features noting other morphologies and the hallmark lack of visible signs of inflammation in most cases [19].

During Brocq's time and since, the nature of pseudopelade of Brocq has been debated [4, 18, 20, 41, 117, 145]. Some consider it a unique clinicopathologic entity, whereas others view it as a variant of certain primary cicatricial alopecias (usually lichen planopilaris and/or discoid lupus erythematosus) or as a nonspecific form of end-stage cicatricial alopecia. Pseudopelade is a term also used to describe burnt out forms of primary cicatricial alopecia. For this reason, some advocate that the term be dispensed with completely.

The confusion results in part from subtly different notions about its clinical presentation, that in turn produce mixed findings on histopathology [4, 18, 117]. Brocq's clinical conception of the condition – a noninflammatory, small and large plaque form of primary cicatrizing alopecia – shows features of lichen planopilaris on histology in a significant proportion of affected individuals [117]. Using the clinical criteria of Braun-Falco et al. [18], derived from cases that could not be otherwise classified and in which "erythema" was observed in a majority at some point during the course of disease, histopathologic features of lichen planopilaris or discoid lupus erythematosus are seen in 33%–69% [4, 18]. Degos et al. [40] extended this thinking even further, stating that pseudopelade was a nonspecific form of multiple types of cicatricial alopecia independent of cause and coined the term *l'état pseudo-peladique* to capture this notion [40]. And yet, despite these findings, there remains a subset of cases that defy classification as another form of cicatricial alopecia. These cases may represent true autonomous disease, but settling the matter will likely require a different and probably molecular-based approach.

11.3.5.2 Epidemiology

For the reasons stated above, it is hard to determine the true epidemiology of pseudopelade of Brocq (if one subscribes to its autonomous existence). Nonetheless, by all accounts the majority of those affected are adults 20 years and older [12, 20]. Reports on sex predilection conflict [18, 20, 145]. Most cases develop in Caucasians, but occurrence in Asians and East Indians has been



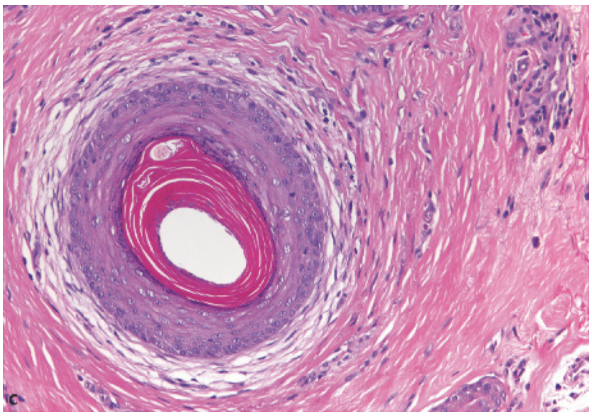


Fig. 11.3a–c Pseudopelade of Brocq. **a** Small atrophic hypopigmented plaque variant in a man with coexisting androgenetic alopecia (from Shapiro, J. Hair loss: principles of diagnosis and management of alopecia. London: Martin Dunitz Ltd.;2002 [153]). **b** Large plaque variant. **c** Histopathology at 20× magnification showing sparse peri-infundibular lymphocytic infiltrate *without* interface alteration, and prominent lamellar fibroplasia

noted as well [145]. It is unclear whether the condition occurs in blacks. There are rare familial cases, with onset of disease in childhood or adolescence [145].

11.3.5.3 Pathogenesis

The cause of disease is unknown. A short, early phase of inflammation, evidenced on histopathology by massive, lymphocyte-mediated follicular destruction by apoptosis, has been proposed to account for the general lack of inflammation seen on exam in most cases [130].

11.3.5.4 Clinical Features

The following description of pseudopelade of Brocq will be based on the original description of Brocq et al. [20, 96].

Pseudopelade of Brocq is limited to the scalp. It is characteristically asymptomatic with no visible signs of inflammation on exam. Thus, the pull test, which yields anagen hairs in acute disease, is an indispensable tool in the assessment of disease activity. Presentations include small, well-demarcated "lentil-like" plaques and coin-sized round, polycyclic or irregularly contoured larger plaques than can measure up to several centimeters in breadth. The small plaque variant is usually multifocal giving a distinctive confetti-like appearance (Fig. 11.3a). The large plaque variant may be single or multiple in number, and not uncommonly involves the central scalp (Fig. 11.3b). A combination of these two morphologies is also seen. Areas of bare skin are usually white or hypopigmented, supple and slightly depressed to touch, and may contain a few unaffected, sometimes kinked, hairs. Extensive disease has been likened to "footsteps in the snow" (*Fr. Transl.)* in appearance [128]. Rarely, a pink to peach-colored blush (similar to that seen in patchy alopecia areata) and fullness are seen in the larger plaque variant, particularly in darker-skinned individuals (authors' observation) [20]. The course of disease is typically slow in progression, with occasional bursts of activity. Overt hair loss may not become apparent for years.

Brocq reported on a single case with coexisting beard involvement [20] as did one of the authors (J.S.) in a second case [103] that, after 2 years, developed colocalizing lichen planus. Other reports of associated lichen planus

fuel the debate about the relation of pseudopelade of Brocq to lichen planopilaris [145].

11.3.5.5 Pathology

Early on, massive lymphocyte-mediated apoptosis of the follicular sheath has been observed [130]. The histopathology of pseudopelade of Brocq is otherwise nonspecific. Suggestive findings include a sparse to moderately dense perivascular and peri-infundibular lymphocytic infiltrate *without* interface alteration, and prominent lamellar fibroplasia in established disease [167] (Fig. 11.3c). The infundibular epithelium becomes atrophic and is eventually entirely destroyed; fusion of the infundibula within a follicular unit may result. Sebaceous glands are lost. Scarred follicular tracts and stranded arrector pili muscles are seen in end-stage disease, as in other forms of primary cicatricial alopecia. Direct immunofluorescence is usually negative. Elastin staining of advanced disease shows a hyalinized dermis with markedly thickened elastic fibers throughout and broad follicular fibrous tracts with intact elastic sheaths [47].

Aspects of these same histopathologic features may be seen in central centrifugal cicatricial alopecia, in bald patches of end-stage primary cicatricial alopecia, and in vertically cut biopsy samples from other primary cicatricial alopecias as a result of missed pathology with this mode of sectioning.

11.3.5.6 Differential Diagnosis

Pseudopelade of Brocq can be confused with patchy alopecia areata, classic lichen planopilaris, and end-stage cicatricial alopecia of disparate origin. A slow inexorable course of noninflammatory, asymptomatic scarring alopecia is diagnostically suggestive.

11.3.5.7 Treatment

Active disease, marked by a positive pull test or extension of hair loss should be treated. Variable success has been reported with topical and intralesional corticosteroids, prednisone, hydroxychloroquine, and isotretinoin, with little detail on protocol [70, 145, 166]. The authors treat pseudopelade of Brocq the same as lichen planopilaris. To facilitate the tracking of treatment response, a target site is chosen. Ideally, it should have measurable alopecia, a positive pull test at the hair-bearing margin, and be visible to the patient who will help in the monitoring process. Size and activity by pull test is followed over time, initially at monthly intervals and adjusted according to the treatment outcomes.

11.3.6 Central Centrifugal Cicatricial Alopecia

Synonyms

hot comb alopecia, follicular degeneration syndrome, chemically induced cosmetic alopecia, pseudopelade in African Americans, central elliptical pseudopelade in Caucasians

Key Features

- Predominantly affects adult black women.
- Usually asymptomatic and noninflammatory.
- Alopecia begins in the midline central scalp, with gradual centrifugal spread over years.
- Histopathology resembles pseudopelade of Brocq.

11.3.6.1 History

This condition was first described by LoPresti et al. in 1968 as “hot comb alopecia” [101], who noted that 51 African-American women had scarring in the central scalp that began in their 20s and 30s and spread outward, inexorably over years. All of the patients shared the practice of using a heated metal comb to straighten their hair. At the end of the article, they briefly remarked on a single case seen in a white female. Price subsequently described a similar condition in young African-American women and remarked on its resemblance to pseudopelade of Brocq both clinically and on histopathology; no unifying hair care practice was found [138]. Sperling and Sau [158] further explored the clinicopathologic aspects of the condition, and found what they believed was the underlying cause; namely, premature inner root sheath desquamation. They renamed the condition “follicular degeneration syndrome” [158]. A debate then ensued as to whether this feature was specific to this entity, as others have noted its occurrence in unrelated primary cicatricial alopecias and only a few follicles are affected within any one biopsy specimen [70, 106, 145]. In 2001, the North American Hair Research Society adopted the term “central centrifugal cicatricial alopecia” to encompass all these entities based on shared morphology [123].

11.3.6.2 Epidemiology

Most reports involve black women and originate from the United States, Africa, and England [30, 101, 119, 158, 159]. Occasionally black men are affected as well [159].

11.3.6.3 Pathogenesis

In the authors' estimation, it remains to be determined if the entities subsumed by the term central centrifugal cicatricial alopecia are the same. First, hot comb alopecia differs from the other conditions both clinically and on histopathology. Second, a causal link that embraces all described forms has not been found. It is assumed that culturally popular hair care practices used by black women account for their connection in disease, but formal epidemiologic studies are lacking to prove this. Moreover, in most individuals cessation of suspect hair grooming practices (chemical and thermal straightening, traction) does not appear to alter the course of disease. Some have since suggested that certain pomades or other hair grooming products may play a role, another supposition that would explain the cohort effect but again is unproven. Olsen [122] has theorized that the condition could represent a form of scarring androgenetic alopecia particular to black women and suggests that a controlled trial using antiandrogen therapy might be warranted to test this hypothesis [122].

11.3.6.4 Clinical Features

Central centrifugal cicatricial alopecia is usually asymptomatic, but scalp tenderness, tingling and itch may be present [30, 158]. In the hot comb variant, the scalp is often sore the first few days after straightening, and first- and even second-degree burns may be seen [101]. Partial hair loss starts in the midline of the mid scalp or vertex as a roughly circular or oval patch, and has a graded drop off moving symmetrically outward. Over years, the alopecic patch progressively enlarges, slowly and centrifugally (Fig. 11.4). The affected scalp skin is flesh-colored, smooth, soft, and pliable to touch. Scattered hairs usually remain within the area of alopecia, and often are short and brittle. Like pseudopelade of Brocq, signs of follicular inflammation are usually absent, but occasionally perifollicular hyperpigmentation is seen. Polytrichia arising from sunken, dilated comedo-like follicular plugs is a common feature seen in the hot comb variant alone. Slow, centrifugal progression is the norm despite the cessation of suspect hair-care practices.



Fig. 11.4 Central centrifugal cicatricial alopecia. Long-standing disease

11.3.6.5 Pathology

In general, findings resemble those seen in pseudopelade of Brocq, and are thus nonspecific [47, 70, 158]. However, Sperling and Sau maintain that premature inner root sheath desquamation (loss of the inner root sheath below the isthmus) is a defining feature of early disease [158].

11.3.6.6 Differential Diagnosis

Central centrifugal cicatricial alopecia must be differentiated from androgenetic alopecia, alopecia areata, traction alopecia, and the large plaque variant of pseudopelade of Brocq. The absence of follicular ostia distinguishes the condition from nonscarring entities with similar morphologies. Distinction of central centrifugal cicatricial alopecia from the large plaque variant of pseudopelade of Brocq is an academic exercise: considerable overlap exists between these two entities. Given this similarity, it is thought provoking to consider whether pseudopelade of Brocq occurs in blacks at all, and, if central centrifugal cicatricial alopecia represents a form of it in this cohort, as has been speculated, why no cases of the lenticular variant have yet been reported.

11.3.6.7 Treatment

Treatment recommendations for central centrifugal cicatricial alopecia are based on anecdote. Symptomatic or spreading disease warrants intervention. Treatment response can be tracked by choosing a target site, as described for pseudopelade of Brocq (Sect. 11.3.5.7). High-potency topical corticosteroids are usually tried first and can help stop progression [30, 138, 159]. Second-line therapy includes monthly injections with triamcinolone acetonide (2.5–5 mg/ml) [30, 138] to the immediate surrounding hair-bearing scalp and remaining hairs within, or oral tetracycline (500 mg twice daily for several months), which can take several months to exert its effect [159]; these can be used additively in partial responders to topical therapy. Weekly shampooing with a corticosteroid-containing agent (e.g., fluocinolone acetonide) can also be used adjunctively [30]. In nonresponders, topical tacrolimus (0.1% ointment twice daily) may be tried. Recently the authors observed modest hair regrowth in one of three women who failed other regimens including topical corticosteroids and/or intralesional triamcinolone injections. Over 6 months of treatment was required to appreciate added fullness, with even greater improvement seen with continued use (unpublished data). There is also brief mention of benefit with hydroxychloroquine (dose not specified) [138]. Lastly, adoption of gentle hair-care practices and natural hairstyles with little traction (e.g., twists, afro) are recommended. For those who are disinclined to alter their habit, longer intervals between these measures should instead be encouraged. Some advocate that hardening gels and sprays be avoided as well [30].

11.3.7 Alopecia Mucinosa

Synonyms
follicular mucinosis

Key Features

- Onset at any age, from infancy onward.
- Conventionally divided into primary, benign, and secondary malignancy-associated (usually mycosis fungoides) types, but longitudinal studies challenge this neat separation.
- Polymorphous presentation; "great mimicker."
- Alopecia, when present, can be nonscarring or scarring.

Key Features

- Histopathology shows mucinous degeneration of the follicular and sebaceous epithelium associated with a perifollicular and perivascular lymphocytic infiltrate.
- No single reliable predictor for development of malignancy.
- Persistent "idiopathic" cases must be followed for malignant change.

11.3.7.1 History

In 1925, Kreibich presented a case of disseminated red to violaceous plaques, some wrinkled in appearance, and others composed of follicular papules or comedo-like lesions; associated pathology showed mucin in the follicular epithelium [91]. In 1957, Pinkus observed the shared feature of lesional alopecia in a six-case series, and named the condition *alopecia mucinosa* [132]. In that same year, Braun-Falco remarked on an association with lymphoreticular malignancies, including mycosis fungoides, in a subset of affected individuals and divided the entity into primary, idiopathic and secondary, lymphoma-related forms [17]. This neat distinction has since been called into question (discussed below) [14].

11.3.7.2 Epidemiology

All ages and races are affected from infancy onward [14, 38, 50, 31, 33]. Incidence in males may be slightly higher (range M:F, 1.4–2.8:1). The most commonly associated malignancy is mycosis fungoides, estimated to occur in 9%–64% [33, 61].

11.3.7.3 Pathogenesis

There are some indications that an antigenic signal originating in the hair follicle incites a folliculotropic T-cell response that in turn stimulates follicular keratinocytes to produce mucin [144, 145]. Possible triggers include *Staphylococcus aureus* infection [76] and certain medications, including some that cause other forms of atypical lymphoid infiltration [104], as well the biologics imatinib and adalimumab [39, 179]. The observation of increased Langerhans cells in the follicular epithelium and the common finding of clonality in the T-cell infiltrate lend further support to the notion of an antigenic

trigger for disease. Scarring results in cases where the follicular epithelium is destroyed by acantholysis, cytolysis, or mucinous degeneration [50, 145].

The inability to predict cases that will go on to develop lymphoma by clinical, pathologic or molecular profiling, other than disease course, has led to the advancement of new theories on the nature of alopecia mucinosa. Some now consider it a variant of follicular mycosis fungoides outright; others a premalignant state like lymphomatoid papulosus, or even as a benign proliferation of lymphocytes (likened to clonal nevi) with a tendency for clonal expansion, that is either self-limited or progressive to malignancy [14, 97].

11.3.7.4 Clinical Features

The head and neck are commonly affected, particularly the eyebrows and scalp [50, 145]. One to multiple lesions may be present. Widespread disease is also seen. Some experience associated pruritus, anhidrosis, or dysesthesia. Common nonscalp morphologies include: indurated, flesh-colored to red, finely scaled plaques with prominent follicular papules, patulous follicular ostia, or comedo-like lesions; and folliculopapules in a diffuse or grouped array. Other colors (e.g., yellow, brown) and morphologies (e.g., nodules, tumors, acneiform papules) also occur. Mixed morphologies are common at presentation. Associated alopecia can be nonscarring or scarring, and is a clue to the diagnosis; however, it is not always present or evident in areas with vellus hair [50, 145]. *Mucinorrhea* manifested by the expression of a clear, gelatinous substance through follicular orifices upon palpation of an indurated lesion or biopsy sample is another helpful diagnostic sign.

When the scalp is involved the hair loss is usually more apparent. Complaints of increased shedding or patchy hair loss are common [50, 145]. Morphologies vary widely. Round or polycyclic patches, diffuse thinning, complete alopecia, black-dot alopecia resembling tinea capitis and reflecting broken hairs, erythematous scaly patches, indurated plaques and soft tumors with patulous ostia, follicular papules, pseudovesicles and pustules have all been described [14, 50, 145]. The authors recently witnessed a case that had overlap features of ophiasis and frontal fibrosing alopecia (Fig. 11.5). Hypopigmentation may be seen in darker-skinned individuals [100]. In one case, *S. aureus* infection was reported in association with crusting [76]. In cases of nonscarring disease, regrowth after remission can take months.

Mycosis fungoides is the predominant malignancy seen in adults; Hodgkin's lymphoma, possibly, in those under 20 years of age [60, 61, 145]. Diagnosis can precede, coincide, or follow the onset of skin lesions. The majority (89%) of those who present with "idiopathic" and then go on to develop overt mycosis fungoides do so within months to 5 years [61]. However, there are isolated reports of a lag lasting one to two decades [14, 98]. Ultimately, there is no single, reliable predictor (including age, extent, location, histopathology, clonality, or treatment response) to help differentiate idiopathic from malignancy-related disease other than disease course [33, 50, 61].



Fig. 11.5 Alopecia mucinosa. This case resembled aspects of alopecia areata and frontal fibrosing alopecia. Note the slight atrophy and perifollicular fine scale

11.3.7.5 Differential Diagnosis

Scalp alopecia mucinosa is a "great mimicker." Likeness to alopecia areata is frequently commented upon. Other presentations resemble telogen effluvium, lichen planopilaris, discoid lupus erythematosus, pseudopelade of Brocq, lichen planus follicularis tumidus, lupus panniculitis, dissecting cellulitis, tinea capitis, Darier's disease, and several other entities as well. Care should be taken to look for nonscalp lesions. Palpation for mucinorrhea should be done. Ultimately, a scalp biopsy is diagnostic.

11.3.7.6 Pathology

Follicular mucinosis is a term that is probably best reserved to describe the histopathologic correlate – a reaction pattern seen in wide range of unrelated disorders [14]. Reticular or cystic degeneration of the outer root sheath and sebaceous epithelium occurs with mucin deposition in the interstices [14, 50, 132]. According to some authors the infundibulum is characteristically affected [14], whereas others note initial involvement of the mid follicle [50, 132]. Panfollicular disease is also

seen. Lymphocytic follicular exocytosis is seen to a varying degree, associated with a focal or diffuse perifollicular and perivascular lymphocytic infiltrate, occasionally admixed with eosinophils [14, 50, 132]. The lymphocytes can appear banal, activated or atypical. Infundibular plugging is a variable feature. In end-stage disease, a residual tract of mucin surrounded by inflammatory cells is seen [133]. Unlike other primary cicatricial alopecias, concentric lamellar fibrosis is absent [167].

Clinical context is essential to interpretation of findings. As mentioned, there is no single, reliable histopathologic or molecular criterion to differentiate primary from secondary lymphoma-associated follicular mucinosis.

11.3.7.7 Treatment

In cases of suspected drug-induced alopecia mucinosa, the drug should be stopped, if possible. Impetiginized lesions should be treated with pathogen-directed antibiotics. Proven malignancy-related disease is also treated accordingly. In the remaining patients, regular surveillance focused on detection of an evolving malignancy, and lymphoma in particular, is essential. Assessment of systemic symptoms and a complete cutaneous and lymph node exam should be done at each visit. The effort should be coordinated with the patient's primary care physician or a hematologist-oncologist. In those with progressive or persistent disease, periodic biopsy samples can aid in tracking. It is important to remember that clonality does not equal malignancy per se [23].

Choice of treatment for "idiopathic" scalp disease is hampered by the small number of reports on the subject and the lack of controls for spontaneous remission (Table 11.3). No one effective treatment has emerged. Suggested first-line therapy is topical corticosteroids and/or monthly intralesional triamcinolone acetonide injections. In nonresponders or those with more extensive disease, a tetracycline may be tried in age-appropriate individuals (e.g., 100 mg minocycline twice daily) [145, 178]. Remission should be apparent within a few months, at which point the drug is tapered to the lowest effective dose required for maintenance. Second-line therapies include isotretinoin (0.5mg/kg daily for 4 months) which may be partially or completely effective [6, 145]; dapsone, which incites rapid resolution in some (100 mg daily, with maintenance); mepacrine (100 mg twice daily, with maintenance) used successfully in one case; and phototherapy [145]. Other alternatives, though not exhaustive, include topical and oral indomethacin, prednisone as a temporizing measure, excision, topical nitrogen mustard, superficial X-ray radiation (used in the remote past), all of which produced mixed outcomes [145].

Table 11.3 Evidence-based ratings of treatments for "idiopathic" alopecia mucinosa

Topical and intralesional corticosteroids	4
Superficial X-ray radiation	4
All other agents	5

11.3.8 Keratosis Follicularis Spinulosa Decalvans (KFSD)

OMIM Number 308800

Synonyms
keratosis pilaris decalvans

Key Features

- Onset in infancy.
- Sporadic or familial.
- Triad of widespread follicular keratosis succeeded by atrophy, cicatricial alopecia of the scalp, and photophobia – variably expressed.
- Females tend to have milder disease.
- Remission can occur during puberty.
- Histopathology shows a "mixed" inflammatory infiltrate in some cases. Follicular plugging, hypergranulosis and neutrophilic spongiosis of the infundibulum and adjacent epidermis occur in acute disease, with perivascular and perifollicular lymphocytic infiltration thereafter.
- Treatment may have to be instituted in childhood to thwart scarring.

11.3.8.1 History

In 1905, Lameris described the first cases as seen in four members of a Dutch family [94]. Siemens later detailed the condition more completely and coined its current name [153].

11.3.8.2 Epidemiology

Keratosis follicularis spinulosa decalvans is rare. Reports originate from Europe and North America [145]. Descriptions are largely of familial cases, but sporadic disease is not uncommon [58] and may be underdiagnosed. Caucasians appear to be largely, if not exclusively, affected.

11.3.8.3 Pathogenesis

Disordered cornification has been shown by ultrastructural analysis [140]. Most affected families have a pattern of inheritance compatible with X-linked transmission [58, 124]. Occurrence in females is thought to reflect random X inactivation, but reports of male-to-male transmission suggest instead that keratosis follicularis is a more complex, genetically heterogeneous disorder. In two families with an X-linked pattern of inheritance, the genetic defect has been localized to the p22.13-p22.2 region of the X chromosome, but in a third, this region was not involved [124]. Recently, a male child with both dosage-sensitive sex reversal and features of KFSD was shown to have duplication of a region just proximal to this candidate locus, overlapping a region of interest in the outerlying pedigree [63]. Contained within this region is a gene that encodes spermidine/spermine N^1-acetyltransferase (*SSAT*). Overexpression of *SSAT* in mice produces features reminiscent of KFSD but somewhat divergent [131]. Further study is needed to determine causality.

11.3.8.4 Clinical Features

In general, KFSD is marked by widespread keratotic follicular papules succeeded by atrophy, cicatricial alopecia of the scalp, and photophobia [28, 145]. The triad is variably expressed. Males are more likely to develop complete, severe disease.

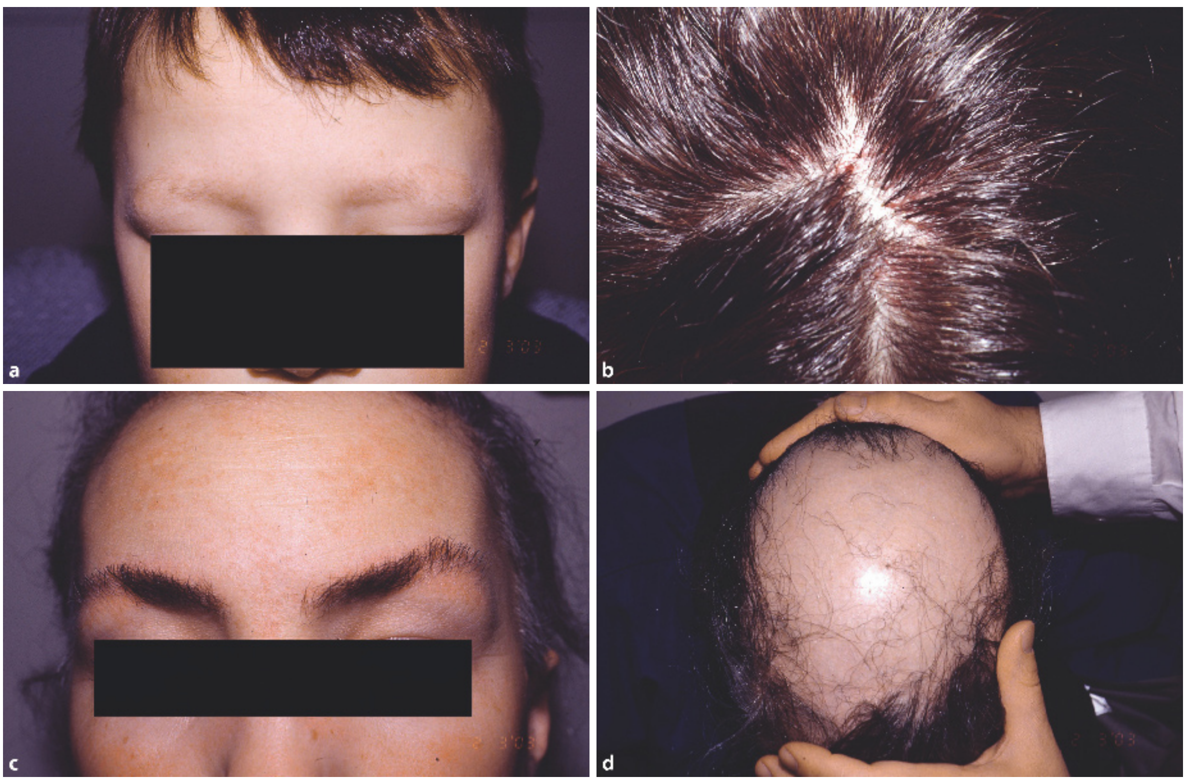


Fig. 11.6a–d Keratosis follicularis spinulosa decalvans as seen in a boy and his mother. (From Ross, EK, Tan E, Shapiro J. Update on primary cicatricial alopecias. J Am Acad Dermatol 2005;53:1-37 [145]). **a** Peri- and inter-follicular erythema and scale along with thinning of the eyebrows in the boy. **b** Associated early scarring alopecia. **c** Facial features in the mother include eyebrow erythema and reddish-tan telangiectatic macules on the forehead and cheeks. **d** Associated extensive, end-stage scarring alopecia

In infancy variably erythematous follicular keratotic papules that resemble keratosis pilaris develop on the cheeks, eyebrows, eyelashes, forehead, and nose [7, 51, 58, 143, 145]. Pruritus or tenderness may be associated. Thereafter, the scalp, neck, extensor arms, and trunk become affected. By early childhood, patchy alopecia of the eyebrows, eyelashes, and scalp develops (Fig. 11.6a,b). The scalp shows perifollicular hyperkeratosis with variable erythema at the edge of cicatrized plaques. Mainly on the face follicular plugs, patulous ostia, and punctuate atrophy appear; red-brown telangiectasias may be seen as well (Fig. 11.6c). In some, both the skin and eye disease regress in the peripubertal period, whereas others experience gradually progression of their skin disease (Fig. 11.6d). In a subset of individuals acute worsening of their scalp disease occurs at this time, heralded by the appearance of follicular pustules at the hair-bearing margin like that seen in folliculitis decalvans. *Staphylococcus aureus* is commonly isolated. Oranje et al. [125] named this form of disease *folliculitis spinulosa decalvans* and considered it a separate entity with a different pattern of inheritance [125] – a point yet to be fully substantiated. Inconstant features of KFSD include keratoderma of the palms and soles (the heels typically), high periungual cuticles, and ichthyotic xerosis [7, 51, 58, 143, 145]. Photophobia, when it occurs, develops with the skin disease, and can regress as the child ages. Conjunctivitis, blepharitis, and ectropion have also been reported. Many affected individuals are atopic.

11

11.3.8.5 Differential Diagnosis

Keratosis follicularis spinulosa decalvans shares features with other genodermatoses characterized by keratosis pilaris, including keratosis pilaris atrophicans faciei and atrophoderma vermiculata (considered by some to be part of the same disease constellation called keratosis pilaris atrophicans), ichthyosis follicularis with alopecia and photophobia (IFAP), and keratosis ichthyosis and deafness (KID). Like KFSD, keratosis pilaris atrophicans faciei and atrophoderma vermiculata are marked by keratotic follicular papules, atrophy, and alopecia, but vary in the distribution, degree of inflammation, and scarring; scalp alopecia is generally only seen in KFSD [143]. Ichthyosis follicularis with alopecia and photophobia shares many features KFSD but the alopecia is present at birth, and is nonscarring and diffuse. Keratosis ichthyosis and deafness syndrome can be distinguished by the presence of striking erythematous hyperkeratotic plaques on the cheeks and extremities, palmoplantar keratoderma that is diffuse and stippled, and sensorineural deafness, usually present at birth. Nail dystrophy, dental caries, and recurrent cutaneous infections are also seen.

11.3.8.6 Pathology

Reports on the pathology of scalp disease in keratosis follicularis spinulosa decalvans are scant. Early on, hyperkeratosis and hypergranulosis affect the infundibulum and isthmus [7]. This is followed by an acute inflammatory phase, marked by neutrophilic spongiosis of the adjacent epidermis, with an acute inflammatory infiltrate and edema of the papillary dermis. Thereafter a sparse perifollicular and perivascular lymphocytic infiltrate is seen and fine collagen bundles and mucin occupy the surrounding stroma. Granulomatous inflammation heralds follicular destruction. The fate of the sebaceous gland remains unclear [145].

11.3.8.7 Treatment

Reports on treatment of scalp disease are limited (Table 11.4). To thwart scarring, intervention in childhood is usually required. The best agent has yet to be identified. A trial of mid- to high-potency topical corticosteroids is recommended first [7, 143]. If after 6–8 weeks hair loss continues, monthly intralesional injections of triamcinolone acetonide starting at 3 mg/ml may be tried in age-appropriate candidates. In nonresponders, oral retinoids are an option to be weighed carefully, avoiding high doses and prolonged use in children and adolescents. Outcomes have been mixed, possibly due to differences in the level of disease activity at the time of intervention [58, 145]. Lasting remission has been reported in two cases of active disease treated with etretinate (0.8 mg/kg) or isotretinoin (0.5mg/kg) daily for 12 weeks; spinous hyperkeratosis was unaffected [145]. It is unknown whether topical retinoids have any effect. Laser epilation should be reserved as a last resort for obvious reasons [145]. Pustular flares, usually associated with *S. aureus*, respond to antibiotics in most [145]. Dapsone (100 mg/day) is a second choice. As in all cases of primary cicatricial alopecia, hair transplantation is an

Table 11.4 Evidence-based ratings for treatment of keratosis follicularis spinulosa decalvans

Topical corticosteroids	4
Intralesional triamcinolone	5
Oral retinoids	5
Laser	5
For pustular disease	
Pathogen-directed oral antibiotics	5
Dapsone	5

option in appropriate candidates with limited burnt out scalp disease (Sect. 11.6), and has been used successfully in a case of eyebrow alopecia [53].

Eye disease should be followed by an ophthalmologist. In one case, low-dose vitamin A subjectively improved photophobia [174]. Genetic counseling is advised as well.

11.3.9 Discoid Lupus Erythematosus

Discoid lupus erythematosus (DLE) affects both the epidermis and the hair follicle and thus cannot be strictly categorized as a form of primary cicatricial alopecia.

Synonyms
chronic cutaneous lupus erythematosus

Key Features

- Onset typically in females between ages of 20 and 40 years.
- Presenting sign of systemic lupus erythematosus in 5%–10%.
- Erythematous plaques with adherent scale and follicular plugs followed by atrophy, dyschromia, and telangiectasias.
- Histology shows interface dermatitis with basal vacuolization affecting follicular and epidermal epithelium, follicular hyperkeratosis, perivascular and periadnexal lymphocytic infiltrate, and dermal mucin. Epidermal atrophy, basement membrane thickening, and dermal fibrosis follow.
- Treat early to thwart scarring and to regrow hair.

11.3.9.1 History

In 1833, Biett described what appears to be the first case of DLE, as later acknowledged by his student Cazenave [32]. Kaposi observed that DLE can occasionally progress to systemic lupus erythematosus [80].

11.3.9.2 Epidemiology

Onset of DLE typically occurs between the ages of 20 and 40 years, predominantly in females (3:2 to 3:1) [154]; 2% are under the age of 10 [113]. Scalp disease is often present at the outset, occurring in 34%–56% of adults [145]. The scalp remains the sole site affected in 11%–58% [35, 52, 145, 177]. All races are affected, but Caucasians and blacks may be particularly prone [46].

11.3.9.3 Pathogenesis

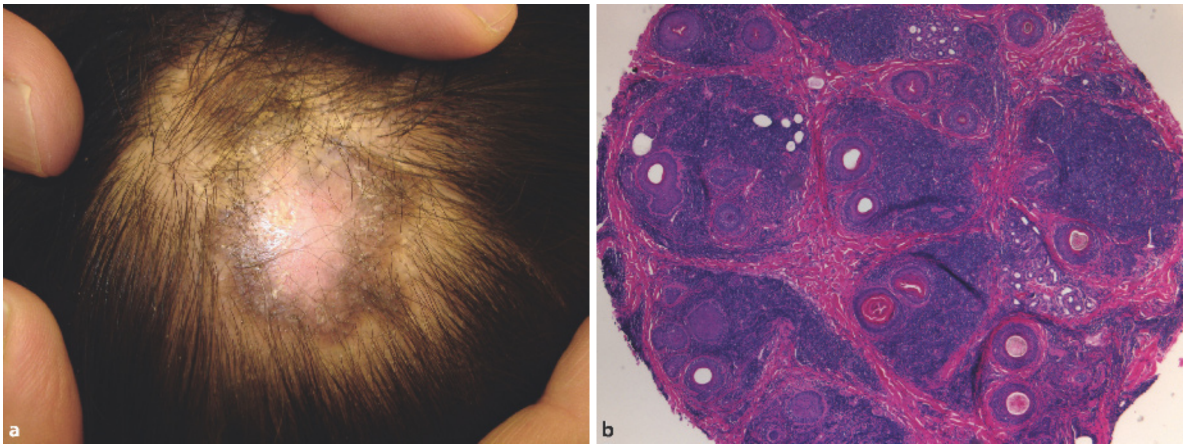
A complex interplay of genetic, environmental and host factors determines expression of disease [46]. In susceptible individuals, ultraviolet radiation is thought to induce keratinocyte apoptosis and immunosuppression followed by an autoreactive inflammatory response, culminating in epithelial destruction. Deficient clearance of apoptotic cells contributes to perpetuation of disease.

Triggers for the development of DLE of the scalp are unknown. The vertex appears to be preferentially affected (72%–87%) [35, 52], which implicates a possible role for sun exposure. However, those with bare areas due to androgenetic alopecia, a history of extensive sun exposure evidenced by solar elastosis on scalp biopsy, or with subjective photosensitivity are not affected to any greater extent than others [177]. Koebnerization is another possible culprit. Discoid lupus erythematosus occurs in areas of excoriation and in the ritual scalp "sorry cuts" of grieving Aboriginal women [145].

11.3.9.4 Clinical Features

Patients usually present within 1 year of onset, and complain of patchy hair loss associated with pruritus, burning, stinging, or tenderness. The vertex scalp is the most common site affected (72%–87%) [35, 52], followed by the parietal and temporal-parietal areas (52%) [52]. A positive pull test for anagen hairs signifies active disease. In early disease, a well-demarcated erythematous papule or small plaque with scale is seen, usually at more than one site [35, 52, 145]. With time, the hair is shed and the lesions thicken, enlarge, and develop adherent scale and follicular plugging (Fig. 11.7a). At this stage, the "carpet tack" sign may be elicited, whereby retraction of the scale reveals keratotic spikes underneath, corresponding to the follicular plugs. In late-stage disease, the center of the lesion is depressed, depigmented, and telangiectatic – characteristic features. Mottled dyschromia may also be seen. In darker skinned individuals the rim of the scar is often hyperpigmented.

Scalp involvement with DLE portends a chronic course, particularly in those with widespread (below the neck) involvement [145, 177]. Recurrences are usually seen in formerly affected scars. Systemic lupus erythematosus develops in about 5%–10% of adults, usually within 1–3 years of diagnosis [29]. Adults with widespread disease and affected children (26%–31%) may be particularly prone [29, 145]. Complications of DLE include ulceration and development of secondary



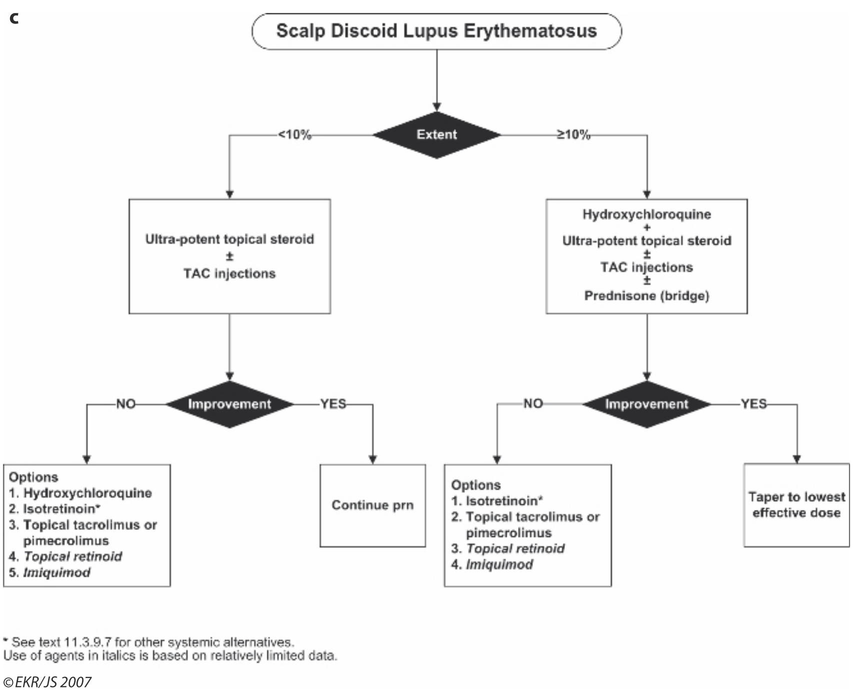


Fig. 11.7a–c Discoid lupus erythematosus. **a** Subacute disease showing a central erythematous scaly patch with follicular keratotic pits, and marginal hyperpigmentation. **b** Histopathology at 4× magnification showing perifollicular, periadnexal and interstitital lymphocytic infiltration in acute disease. **c** Treatment algorithm

squamous cell carcinoma that can be life-threatening if left unchecked.

11.3.9.5 Pathology

Acute DLE is characterized by vacuolar interface alteration of the upper follicle and epidermis associated with adjacent dyskeratotic keratinocytes and a superficial and deep dermal perivascular and perieccrine predominantly lymphocytic infiltrate [167] (Fig. 11.7b). Civatte bodies are less common than in lichen planopilaris. Sebaceous epithelium is atrophied or absent. Mucin is interspersed in the reticular dermis. As the lesion progresses, orthokeratotic hyperkeratosis of the follicular ostia (follicular plugging) and epidermal atrophy become apparent. The basement membrane is thickened, and pigment incontinence and dermal fibrosis are present. Concentric lamellar fibrosis is an end-stage finding. Elastic tissue staining of advanced disease reveals diffuse dermal scarring and no evident follicular elastic sheath [47]. On direct immunofluorescence, diffuse granular deposition principally of IgG or IgM with C3 along the dermoepidermal junction is characteristic.

11.3.9.6 Differential Diagnosis

Active scalp DLE can resemble psoriasis, inflammatory seborrheic dermatitis, tinea capitis, alopecia mucinosa, and Darier's disease. A search for DLE elsewhere on the body or for coexisting signs of systemic lupus is essential. End-stage scalp DLE can be hard to distinguish from other forms of scarring alopecia, but residual dyschromia, follicular plugging and telangiectasias are suggestive.

11.3.9.7 Treatment

The patient should be regularly assessed for signs and symptoms of systemic involvement by exam and screening laboratory tests. Sun-protective measures should be reviewed. Smoking should be discouraged, or at least lessened [29]. Scratching, picking, and traumatic hair-grooming practices should be minimized because of the potential risk of koebnerization. Early biopsy of hyperkeratotic or ulcerated treatment-resistant focus is imperative to rule out secondary squamous cell carcinoma development; prompt aggressive treatment is needed in those with positive findings.

Active discoid lupus should be treated early and vigorously because the hair loss is potentially reversible (unlike in most other types of primary cicatricial alopecias) (Fig. 11.7c, Table 11.5). Localized disease is first treated with high-potency topical corticosteroids and/or intralesional injections of triamcinolone acetonide (3–10 mg/day every 4–6 weeks; to include recent alopecic sites) – often effective within weeks [145]. Second-line or adjunctive topical agents include calcineurin inhibitors [72, 145, 169], retinoids [145, 149], and imiquimod with mixed outcomes, but including remission and hair regrowth in some [145]. The authors recommend starting with tacrolimus 0.1% ointment or pimecrolimus 1% cream twice daily for a 4- to 8-week trial in those with nonhyperkeratotic lesions; compounding with an ultrapotent corticosteroid (0.3% tacrolimus ointment in 0.05% clobetasol propionate ointment, twice daily) [145] is another option. Improvement should be seen within a few weeks, and hair regrowth within 8 weeks. Maintenance therapy is usually required; attempts to wean off the medication should be tried, given the as yet unproven risk of carcinogenicity with long-term use. Isolated reports of facial DLE resolution with tretinoin (0.05% cream nightly ×3 months), and tazarotene (0.05% gel nightly for "months") are also noteworthy [145, 149] as is topical imiquimod, which induced remission in a case of scalp DLE (5% cream daily for 3 weeks, for "2 cycles") [145].

Table 11.5 Evidence-based ratings for treatment of discoid lupus erythematosus[b]

Topical agents	
Corticosteroids	1
Calcineurin inhibitors	3
Retinoids (tretinoin, tazarotene)	5
Imiquimod	5
Intralesional triamcinolone	2
Systemic agents	
Antimalarials	2
Retinoids	
Acitretin	2
Isotretinoin	3

[b] The reader is referred to several excellent reviews on evidence-based systemic therapies, [29, 77, 175]

Discoid lupus erythematosus that is rapidly advancing, extensive, disfiguring or refractory to topical treatment requires the use of a systemic agent [29, 145]. Antimalarials are first line, and often highly effective. Hydroxychloroquine (200–400 mg/day or 200 mg twice daily in adults or 4–6 mg/kg per day in children) is usually tried first due to fewer side-effects than with other antimalarials. Improvement may not be seen for 4–8 weeks, and may require "bridge" therapy with prednisone (1 mg/kg per day, tapered over 8 weeks). Cigarette smoking can reduce efficacy. By 3–6 months, the degree of benefit is usually apparent; quinacrine (100 mg/day) can be added if the response is suboptimal [145]. Retinoids are second line, due to the greater likelihood of side-effects [145]. Isotretinoin (40 mg twice daily or 1 mg/kg per day) is preferred over acitretin because of the lower risk of telogen effluvium and shorter half-life, of obvious importance to childbearing women who make up a significant proportion of affected individuals. Response is often rapid and may not require bridge therapy with prednisone, but the effect may not be durable. In those who do benefit, sustained use is required. Thus, oral retinoids may be best used to check acute disease or as an adjunctive measure until control of disease is established. Alternatively, low-dose therapy (10–40 mg daily) may be used to maintain remission.

Several other systemic therapies have been advocated with varying efficacy, and little is known about their impact on scalp disease [29, 77, 145, 175]. These include, among other agents, dapsone, mycophenolate mofetil, methotrexate, azathioprine, clofazimine, gold, salicylate bismuth, vitamin E and derivatives, systemic and intra-

lesional interferon-α2, monoclonal anti-CD4 antibodies. Low-dose thalidomide is a highly effective in those with refractory disease, but fraught with potentially debilitating side-effects. The reader is referred to several excellent reviews for specifics [29, 77, 175].

Treatment of DLE with vascular lasers (pulsed dye, argon) is controversial. In a study on eight subjects, one of whom had scalp disease (specifics not provided), a roughly 60% clearance rate was observed [8].

End-stage disease can be surgically excised to improve cosmesis [145]. Koebnerization is a risk that may be minimized with use of intercurrent systemic therapy such as hydroxychloroquine.

11.4 Neutrophilic Disorders

11.4.1 Folliculitis Decalvans

Key Features

- Adult onset.
- Pruritus, pain and tenderness may be present.
- Irregularly bordered and round depigmented alopecic patches marginated by follicular pustules, erythema and/or crusts.
- *Staphylococcus aureus* commonly cultured from pustules.
- Histopathology shows acneiform dilation of the infundibulum associated with intra- and peri-follicular neutrophils, followed by a mixed lymphoplasmacytic, neutrophilic, and granulomatous infiltrate with minor abscess formation.

11.4.1.1 History

In 1888, Quinquaud described the first case of folliculitis decalvans, characterized by several coin-sized, atrophic, alopecic plaques surrounded by pinpoint follicular erythema, pustules, and crusts in the hair-bearing margin [142].

11.4.1.2 Epidemiology

Folliculitis decalvans accounts for 11%–20% of all primary cicatricial alopecias encountered in the academic and hair subspecialty setting, and is the most common cause of neutrophilic disease [166, 171, 176]. Young and middle-aged adults of both sexes are typically affected. Familial occurrence is rare, but has been reported in identical twins and in a family with defective cell-mediated immunity [145].

11.4.1.3 Pathogenesis

The pathogenesis of folliculitis decalvans is unknown. The frequent isolation of *S. aureus* from pustules has led some to posit a causal role, variously attributed to superantigen production, intracellular persistence within phagocytes, or host hypersensitivity [22, 44, 136]. Others suggest that the bacterial infection is secondary. Most affected individuals have no immune abnormality, and are not susceptible to bacterial infections elsewhere on the body.

11.4.1.4 Clinical Features

Folliculitis decalvans begins with pinpoint erythematous follicular papules or pustules in groups [16, 96, 145]. Itching, pain, and tenderness may present. Small 2- to 5-mm hemorrhagic crusts ensue (Fig. 11.8a,b). Eventually round or irregularly shaped, shiny, depigmented, subtly atrophic areas of near-complete alopecia develop, with active disease seen at the hair-bearing periphery where it can appear as a "zone of folliculitis." Within the areas of scar, small red macules that mark the sites of follicular destruction may remain, to eventually fade with time. Episodic outbreaks occur at disparate sites, and result in patchy hair loss. In some, the patches coalesce into broad, impressive areas of hair loss. The course of disease is generally chronic and slowly progressive. Rarely, extra-scalp sites may be affected including the face, beard, and the nape of the neck; pubic and axillary involvement has also been noted [16] although other diagnoses might better apply.

Tufted folliculitis – a folliculitis of multiple hairs (5–20), positive for *S. aureus*, that emerge from a common, annealed follicular ostium – is an associated finding in some cases (Fig. 11.8c). When extensive, it can resemble "dolly hair." Most authors consider tufted folliculitis a nonspecific feature seen in different types of cicatricial alopecias, but a resolute few argue that it is specific to folliculitis decalvans.

11.4.1.5 Pathology

Biopsy of a pustule at the hair-bearing margin reveals acneiform dilatation of the follicular infundibulum, associated with an intra- and peri-follicular neutrophilic infiltrate [70, 145, 167]. In more advanced lesions, the

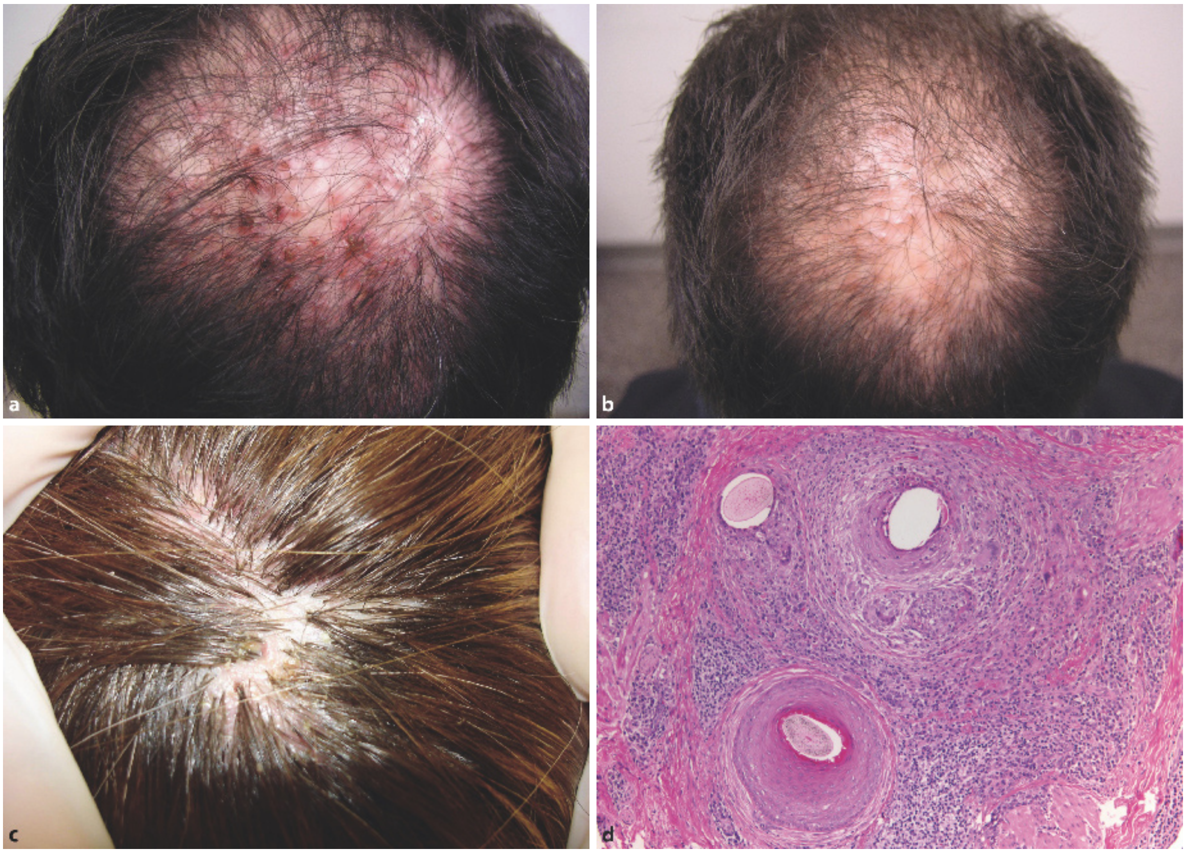


Fig. 11.8a–e Folliculitis decalvans. **a** Subacute disease showing hemorrhagic crusts at former sites of pustules at the advancing edge of scarring alopecia. **b** Appearance of disease after 4 weeks of oral cephalexin and topical mupirocin ointment. **c** Tufted folliculitis. **d** Histopathology at 10× showing an peri- and intra-follicular infiltrate of neutrophils (mid, upper follicle) surrounded by a mixed infiltrate mainly comprised of neutrophils, with some plasma cells and giant cells interspersed. **e** see next page

infiltrate becomes mixed (neutrophils, lymphocytes, and plasma cells), and is usually limited to the upper follicle but not uncommonly involves the entire length (Fig. 11.8d). Abscess formation is less prominent than in perifolliculitis capitis abscedens et suffodiens, and sinus tracts are absent. Adventitial fibrosis is present around remaining follicles. Hair shaft granulomas and vertical stele mark end-stage disease as in most other forms of primary cicatricial alopecia.

11.4.1.6 Differential Diagnosis

Early pustular disease grossly resembles conventional bacterial folliculitis, but the adjacent scarring is dissuasive. In its crusted form, folliculitis decalvans can resemble acne necrotica varioliformis, but is not limited to the frontal scalp and the scars are not pock like. There is some shared overlap with folliculitis spinulosa decalvans but folliculitis decalvans is highly unlikely to be inherited, develops in adulthood, and lacks extracutaneous features.

11.4.1.7 Treatment (Fig. 11.8e, Table 11.6)

The patient should be assessed for any symptoms and signs of immunodeficiency, an infrequent finding. Pustules should be cultured and pathogen-directed antibiotic therapy instituted. Rifampin is probably the best treatment option [136], but because of its side-effect profile a first-generation cephalosporin, semisynthetic penicillin, or tetracycline should be tried first [145]. In general, relief is temporary and relapse is common with discontinuation. The addition of topical mupirocin (authors' observation), topical corticosteroid, intralesional injections of triamcinolone acetonide (10 mg/ml every month, J.S.), or even a short-course of prednisone in rapidly advancing disease can improve outcome [145]. Steroids alone appear to have little effect.

e

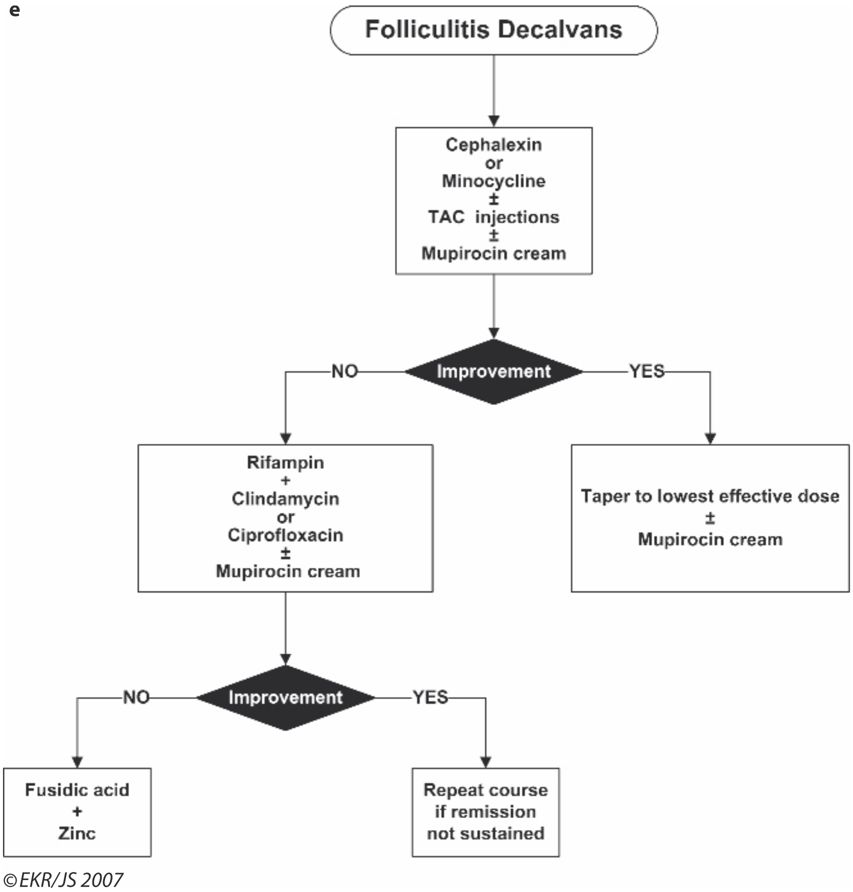


Fig. 11.8a–e (*continued*) Folliculitis decalvans. **e** Treatment algorithm

Rifampin is indicated in the event these measures fail. Its greater efficacy is thought to be due to excellent intracellular penetration, its bactericidal action, and possibly to immunomodulatory properties as well. Moreover, it can eliminate the carriage state of *S. aureus*. Typically, high-dose therapy (300 mg twice daily) is given for 10 weeks along with a second antibiotic to prevent bacterial resistance with monotherapy [136]. Clindamycin (300 mg PO twice daily) is a common choice, but successful outcomes with ciprofloxacin, clarithromycin, or a tetracycline have also been reported [22, 136]. Between 33% and 56% of subjects will have a durable treatment response, lasting between 2 and 22 months. Others require a second and third course. Isolated reports of success with rifampin and topical mupirocin, or with topical 2% erythromycin and oral zinc sulfate are noteworthy, and deserve further investigation [145].

Third-line options include fusidic acid, particularly when combined with zinc (1,500 mg fusidic acid QD ×3 weeks, 1.5% fusidic acid cream ×2 weeks, with oral zinc sulfate 400 mg QD for 6 months; followed by 200 mg zinc QD maintenance therapy) [1, 16, 44, 145] and dapsone (75–100 mg daily ×1–2 months, followed by 25 mg/day maintenance therapy) [126] – both of which can induce long-lasting remission in some individuals. There is also an isolated report of improvement after shaving [145]. Lastly, if the desire to alleviate symptoms (burning, pruritus or pain) is far greater than the desire to retain hair,

Table 11.6 Evidence-based ratings of treatment for folliculitis decalvans

Antibiotics, oral	
Conventional	4
Rifampin + clindamycin	3
Corticosteroids	
Topical	5
Intralesional	5
Oral	5
Fusidic acid + zinc	5
Dapsone	5

laser-assisted trichothermolysis is an option [127]. This is generally more appealing to men than women.

Empiric, periodic treatment of bacterial carriage sites with topical mupirocin in those with persistent disease is advocated by the authors and others [145].

11.4.2 Perifolliculitis Abscedens et Suffodiens

Synonyms
dissecting cellulitis, dissecting folliculitis

Key Features

- Typically affects young adult black males.
- Painful, multifocal bulbous nodules and boggy plaques.
- Associated with acne conglobata and hidradenitis suppurativa in around one-third.
- Risk factor for HLA B27-negative spondyloarthropathy, particularly in blacks.
- On histopathology, acneiform dilatation of the infundibulum with intra- and peri-follicular neutrophils, followed by deep-seated abscess and sinus tract formation.
- Potentially reversible hair loss with prompt therapeutic intervention.

11.4.2.1 History

This condition was first described by Spitzer in 1903, who reported a case associated with acne conglobata [161].

11.4.2.2 Epidemiology

The vast majority of those affected are young black men, with onset between the age of 18 and 40 years [116, 145]. About 10% of cases involve Caucasian males, and even less frequently females, children, and Asians [85, 145]. Familial occurrence is rare.

11.4.2.3 Pathogenesis

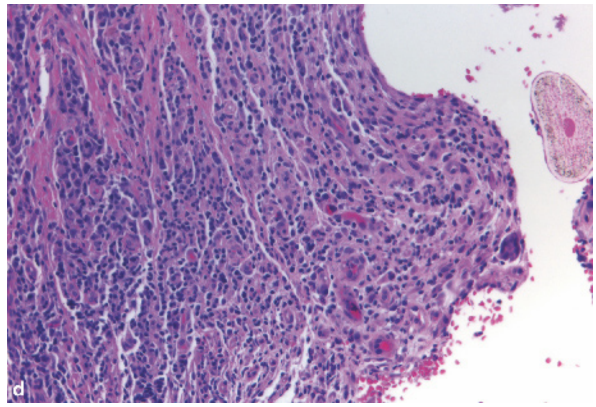
Despite its alternate moniker, perifolliculitis capitis abscedens et suffodiens is not a form of cellulitis. It is considered part of the follicular occlusion triad, along with acne conglobata and hidradenitis suppurativa. A defect in follicular keratinization leading to poral obstruction, secondary bacterial infection, and an exuberant inflammatory response with abscess formation is postulated to occur [109, 164]. However, aerobic cultures of aspirated scalp lesions are often aseptic, and response to antibiotic therapy is usually disappointing. A recent case report suggested that commensal *an*aerobic bacteria may play a pathogenetic role, but further study is needed [21].





Fig. 11.9a–e Perifolliculitis capitis abscedens et suffodiens. **a** Large boggy plaque. **b** Multifocal disease in a man with vertex androgenetic alopecia (From Ross, EK, Tan E, Shapiro J. Update on primary cicatricial alopecias. J Am Acad Dermatol 2005;53:1-37 [145]). **c–e** *see next page*





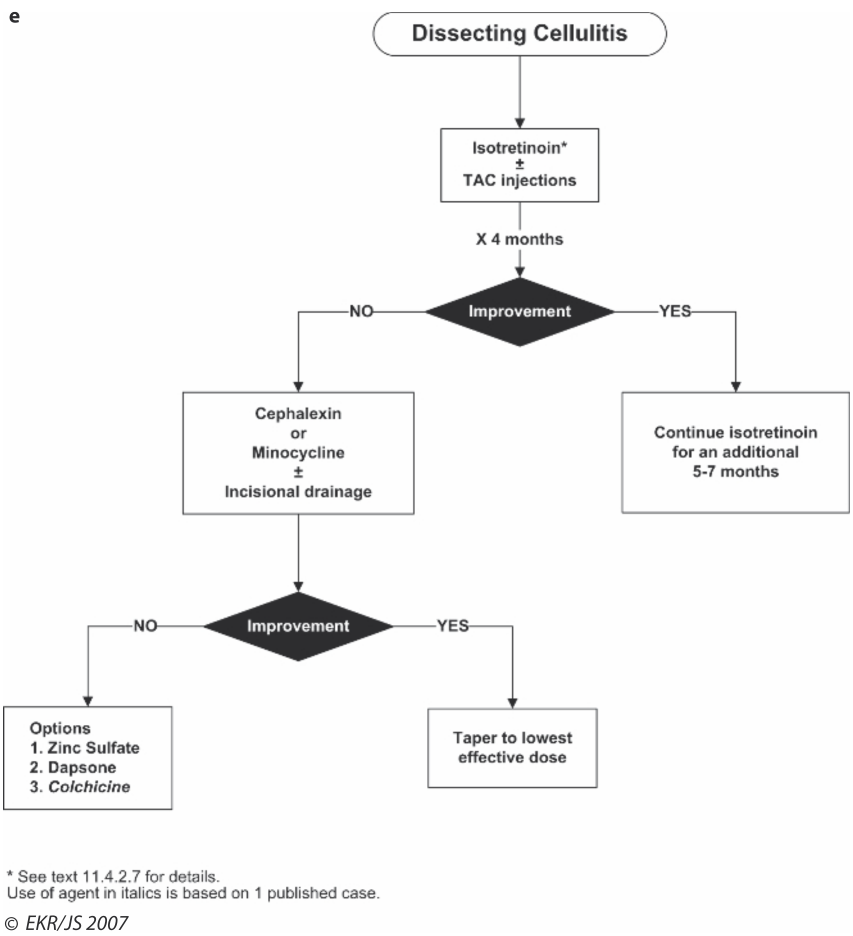


Fig. 11.9a–e (*continued*) Perifolliculitis capitis abscedens et suffodiens. **c** Same man after 4 months of oral isotretinoin (40 mg TID); intralesional triamcinolone acetonide injections were used in the interim to help ease discomfort (From Ross, EK, Tan E, Shapiro J. Update on primary cicatricial alopecias. J Am Acad Dermatol 2005;53:1-37 [145]). **d** Histopathology at 20× showing a sinus tract within which is contained a hair shaft, and surrounding abscess comprised of a mixed infiltrate. **e** Treatment algorithm

11.4.2.4 Clinical Features

Active disease is clinically distinct. Multifocal involvement is common. Initially follicular pustules develop, typically on the occipital or vertex scalp [145, 168]. Characteristic, variably painful, bulbous, erythematous to flesh-colored, fluctuant nodules quickly follow, that may undergo spontaneous suppuration (Fig. 11.9a,b). Hairs overlying the nodules can be easily epilated. Alopecia ensues. Keratotic follicular plugs are evident in some. Nodules can enlarge to form curvilinear boggy plaques or ridges, and can interconnect to impart a cerebriform appearance to the scalp. Cervical and occipital lymphadenopathy may be associated. Without early, aggressive

treatment the hair loss will become permanent, leaving broad scars. The scars may be atrophic, hypertrophic or keloidal, and often have polytrichia. The course of disease is chronic and relapsing, but may be self-limited. Rare complications include the development of potentially life-threatening squamous cell carcinoma, and secondary osteomyelitis [145]. An elevated serum erythrocyte sedimentation rate is occasionally noted.

In about one-third of cases, perifolliculitis capitis abscedens et suffodiens occurs in conjunction with other conditions seen in the follicular occlusion triad [116]. This presentation is a risk factor for the development of HLA B27-negative spondyloarthropathy, characterized by episodic oligoarthropathy of large joints and/or axial arthritis [145, 168]. Black men are particularly susceptible. Active skin disease usually precedes the onset of arthritis by years, and parallels flares. Uncommon associations include other forms of arthritis (perifolliculitis capitis abscedens et suffodiens-associated polyarticular arthritis with sternoclavicular hyperostosis and SAPHO syndrome) and marginal keratitis [145].

11.4.2.5 Pathology

Like folliculitis decalvans, early perifolliculitis capitis abscedens et suffodiens is marked by acneiform distention of the follicular infundibulum with an intra- and peri-follicular neutrophilic infiltrate [157, 167]. A prominent, deep-seated abscess then forms in the adventitial dermis and subcutis, comprised of a mixed infiltrate rich in plasma cells (Fig. 11.9d). Vascular proliferation becomes more evident as the inflammation progresses. An increase in telogen/catagen hairs is seen. Eventually the abscess becomes partly lined with squamous epithelium or sinus tracts. Dense surrounding dermal fibrosis follows, with destruction of the hair follicle. Unlike many of the other primary cicatricial alopecias, sebaceous glands persist until late in disease. End-stage disease shows extensive interstitial and subcutaneous fibrosis surrounding sinus tracts. Sinus tracts distinguish perifolliculitis capitis abscedens et suffodiens from the other primary cicatricial alopecias.

11.4.2.6 Differential Diagnosis

The characteristic appearance of perifolliculitis capitis abscedens et suffodiens usually makes clinical diagnosis straightforward. However, there are a few reports of tinea capitis that closely mimicked perifolliculitis capitis abscedens et suffodiens [145]. The authors witnessed such a case in a young East Indian girl and believe that prior use of topical corticosteroids played a role in the development of this variant, akin to Majocchi's. A high index of suspicion is warranted in females, children, and in those with treatment-refractory disease. Diagnosis may require a scalp biopsy for fungal culture, as potassium hydroxide smears and fungal stains of tissue can be negative [155]. There are also single case reports of *Mycobacterium fortuitum* infection and fatal follicular mycosis fungoides with follicular mucinosis that resembled perifolliculitis abscedens et suffodiens [54, 62]. In the latter case, clues to its malignant nature included the presence of nonscalp lesions with follicular accentuation, and marked lymphadenopathy.

11.4.2.7 Treatment (Fig. 11.9e, Table 11.7)

Until isotretinoin became available, perifolliculitis capitis abscedens and suffodiens was notoriously difficult to treat (Fig. 11.9e). Since the hair loss is potentially reversible in this condition, it is the authors' opinion that it should be tried first (Fig. 11.9c); however, because of its side-effect profile, in limited disease (<10%) one may first choose to start with an oral antibiotic (e.g., tetracycline or erythromycin) for a 4- to 6-week trial [145]. Monthly intralesional triamcinolone acetonide injections and periodic incision and drainage of painful lesions may be done adjunctively if needed. Severe, painful disease can be checked within days with prednisone (0.5–1 mg/kg per day), which can be given over 3 weeks in a tapered fashion and then used at low (5 mg) alternate-day dosing to sustain the effect until control with a

Table 11.7 Evidence-based ratings of treatment for perifolliculitis capitis abscedens et suffodiens

Oral antibiotics	4
Corticosteroids	
Intralesional triamcinolone acetonide	4
Prednisone	5
Incision and drainage	4
Isotretinoin	
Oral	4
Topical	5
Other systemic agents	
Zn^{2+}/Zinc sulfate	4
Dapsone	5
Colchicine	5
Cyproterone acetate and minocycline	5

steroid-sparing agent is achieved. Although benefit can be derived from these different therapeutic modalities, the response is often transient and suboptimal.

Isotretinoin may be instituted if the above measures fail after 4–8 weeks. Disease-free remission up to 2.5 years has been reported with its use [145, 148]. Associated spondyloarthropathy may dramatically improve in kind [99]. Treatment starts with 1 mg/kg per day for 4 months, at which point flattening of the nodules should be evident, and is followed by 0.75-1 mg/kg per day dosing for an additional 5–7 months. The extent of hair regrowth seen at the end of treatment depends on the stage of disease at baseline. Treatment failures have been attributed to use of lower doses and shorter treatment duration. Occasionally, patients require a second course. An isolated case report of prolonged remission with topical 0.05% isotretinoin gel used in combination with topical clindamycin (frequency not specified) for 8 weeks followed by isotretinoin gel alone for 8 months is noteworthy, and deserving of further study [82]. While waiting for the isotretinoin to take effect, a foothold on disease activity can be gained by using monthly intralesional triamcinolone acetonide injections, or prednisone in severe disease (as discussed above), along with antibacterial soaps, and periodic drainage of painful nodules when indicated [145, 150].

Third-line options include oral zinc sulfate, with some, but not all, authors reporting long-standing remission with use (90 mg of Zn^{2+} TID ×12 weeks then 45 mg TID for an additional 10 weeks) [13, 85, 148]; dapsone (regimen not specified), with similar conflicting reports of benefit; colchicine (0.6 g twice daily), which produced moderate improvement in one case; and combination cyproterone acetate and minocycline in females, based on a single case report of effectiveness [145].

In willing patients with medically intractable, symptomatic or cosmetically disfiguring disease, follicular destruction by trichothermolysis using laser is an option [145]. Radiation-induced epilation using modern methods is a recently described alternative, but may have a greater associated risk of secondary squamous cell carcinoma [36]. Surgical excision using the carbon dioxide laser or a conventional approach has also been done [145].

11.5 Mixed Cicatricial Alopecia

11.5.1 Acne Keloidalis

Synonyms

acne keloidalis nuchae, folliculitis keloidalis, folliculitis keloidalis nuchae

Key Features

- Typically affects post-pubertal black males under age 40.
- Occipital scalp and nape of the neck.
- Papulopustular or plaque/tumor keloid-like variants.
- Histologically, perifollicular and follicular inflammation composed of neutrophils or lymphocytes early on and a chronic mixed inflammation with plasma cells later, most pronounced at the level of the sebaceous gland.

11.5.1.1 History

This entity was probably initially recognized by Hebra and Alibert, but was first described by Kaposi in 1869: a 30-year-old male presented with a chronic, broad, keloid-like, painful and periodically pruritic “tubercle” with polytrichia on the nape of the neck, surrounded by pinhead-sized firm papules in the occipital hairline and below [3, 81].

11.5.1.2 Epidemiology

Post-pubertal black males under age 40 are typically affected, with a mean age at onset of 29 years [2]. Non-black males and black females can also be affected, but less commonly [57, 74]. Disease prevalence in the general population is unknown, but among studies with 1000 or more black attendees seen in general dermatology clinics around the world, acne keloidalis accounts for between 0.45% and 3.7% of all diagnoses rendered [2, 45, 57, 59, 120, 121].

11.5.1.3 Pathogenesis

The term *acne keloidalis* is a misnomer. The condition is not related to acne vulgaris, and the scars are hypertrophic rather than keloidal. A unique property of the curved, kinked or thick-shafted hair follicle, common among blacks, is thought to play a role in the development of disease, in association with factors that arise once puberty is reached [43, 145]. Chronic trauma to the site, in the form of scratching, picking, rubbing from shirt collars, and closely shaved hair cuts may also be contributory. Indeed, some have likened acne keloidalis to a kind of papular lichen simplex chronicus to which blacks are particularly prone [25]. The finding of increased mast cell density in occipital scalp [59] is an

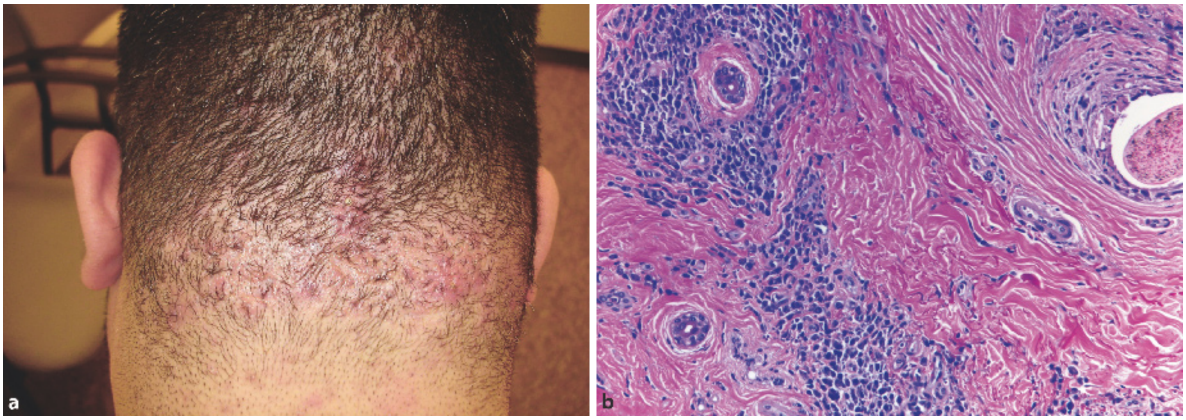


Fig. 11.10a,b Acne keloidalis varioliformis. **a** Papulopustular disease associated with scarring. **b** Histopathology of advanced disease at 20× shows a mixed infiltrate surrounding follicles associated with dermal fibrosis

interesting corollary to this theory. Demodex, *Staphylococcus*, and seborrheic dermatitis often coexist, but are thought to play a secondary role by most [145]. Autoimmunity, higher fasting testosterone levels, and transepithelial elimination of hair are among some of the other proposed theories for which there is limited or contradictory evidence [42, 59, 145]. Further clues to pathogenesis may be derived from sporadic occurrence of drug-induced acne keloidalis in white males – largely associated with ciclosporin, but also with diphenylhydantoin and carbamazepine in one case [145].

The still popular notion that acne nuchae keloidalis is the scalp equivalent of pseudofolliculitis barbae is not substantiated by histopathological findings [160] or by the occurrence of disease in subjects who have never worn closely cropped hair styles [84].

11.5.1.4 Clinical Features

In early disease, the patient usually complains of "pimples" or "bumps" on the occiput and nape that are often pruritic and sometimes painful [43, 83]. On occasion, the vertex is also involved. Initially, scattered small, smooth, flesh-colored, pink, or reddish brown, variably crusted papules or pustules are seen (Fig. 11.10a). A hair may be seen to pierce the papule. Umbilication is also observed. The extent ranges from a few papules to 25 or more. In some individuals, the papules enlarge to form nodules, broad keloid-like plaques, or, rarely, large sclerotic tumors. Pustules, undermining abscesses, tufted hair folliculitis, sinuses with foul-smelling discharge, and pain can complicate this more severe form of disease. Acne keloidalis is a chronic condition, unlikely to remit without therapeutic intervention.

11.5.1.5 Pathology

Descriptions of early disease conflict and may relate to the form of disease biopsied (e.g., pustular or papular). An acute neutrophilic or lymphocytic folliculitis and/or perifolliculitis pronounced at the level of the deep infundibulum and isthmus, and a chronic lymphoplasmacytic perifolliculitis affecting this same region have been observed [73, 160, 167]. Acneiform dilatation may also be apparent. The sebaceous gland is atrophied or absent early on. At the level of the isthmus, the epithelium may be thinned and lamellar fibroplasia evident. With ongoing disease, focal or complete follicular epithelial destruction occurs and granulomatous inflammation or microabscesses form around extruded fragments of hair. Chronic inflammation with numerous plasma cells and significant dermal fibrosis ensues (Fig. 11.10b).

11.5.1.6 Differential Diagnosis

Acne mechanica, bacterial folliculitis, and molluscum contagiosa may occasionally be mistaken for acne keloidalis.

11.5.1.7 Treatment (Table 11.8)

In general, limited nonplaque disease is managed with medical therapy, whereas treatment-refractory and plaque/tumor disease require excision. Close shaving of the area, as well as picking and scratching should be avoided to minimize potential flares and further spread of disease.

Early pustular and papular disease should be treated promptly and aggressively to try to induce resolu-

Table 11.8 Evidence-based ratings of treatments for acne keloidalis

Antibiotics	
Topical	3
Oral	4
Corticosteroids	
Topical	3
Intralesional triamcinolone	5
Antiseptic soaps	5
Other topical agents	
Imiquimod	5
Pimecrolimus	5
Tretinoin + an addition agent	5
Oral isotretinoin	5
Cryotherapy	5
Laser epilation	5
Excision	
Punch excision	5
Cold steel knife	2
Carbon dioxide laser assisted	4

11

tion. Antibiotics alone may be effective, and should be pathogen-directed where possible. In mild to moderate disease (arbitrarily defined as under 20 lesions), topical clindamycin is the first agent of choice. In a study of ten subjects treated with 1% clindamycin lotion twice daily (undisclosed duration) improvement occurred in all subjects and there was complete clearance in 30% excluding larger keloidal lesions [37]. In more extensive disease, an oral antibiotic may be required. Several authors have noted particular benefit with the oral tetracyclines [105, 160], generally used at acne doses, but the penicillins and cephalosporins may also be effective [145]. Adjunctive use of antibiotic soaps has been advocated. In partial responders with papular disease, the addition of a topical corticosteroid may further improve outcome [37]. Used alone a modest improvement can be expected (pulsed clobetasol propionate 0.05% foam twice daily, with a 2-week on/off regimen for 8 weeks; flares may occur during off times) [31]. In small nodular or more fibrotic papular disease, intralesional injections of triamcinolone acetonide (10–40 mg/ml every 4 weeks) is indicated. Care should be taken to use the lowest effective strength possible to avoid depigmentation. A topical anesthetic pretreatment can blunt the pain with injection, or one can use a needle-free device. Alternative treatments based on limited data include imiquimod (QD or 5 days/week ×8 weeks) [10, 83] with a 28% average reduction in lesion number [10] compared to a 17% reduction with topical pimecrolimus (BID ×8 weeks) [10]; and oral isotretinoin, with mixed outcomes reported ranging from no benefit to remarkable improvement [105, 163]. Topical tretinoin combinations (e.g., topical retinoic acid gel mixed with a corticosteroid gel at night) have variable benefit [83, 105, 151]. In those with papular disease that is unresponsive to medical therapy, cryotherapy is an option [105] (two freeze-thaw cycles of 20 s each) [83]; discomfort, drainage and the possibility of hypopigmentation for months, or even permanent depigmentation if done too vigorously are somewhat prohibitive [83]. Lesional punch excision deep past the follicular bulb into the subcutaneous layer can also be done, leaving the surgical wound to heal secondarily [83]. Most recently, lesional laser epilation has been touted for refractory small papular disease, with over 90% clearance reported in two East Indian males after four treatments using the diode laser at 4- to 6-week intervals, in conjunction with topical tretinoin 0.025% cream and betamethasone dipropionate 0.05% cream at night [151].

In patients with extensive cosmetically bothersome or symptomatic plaque disease, surgical excision with a cold steel blade is the only treatment option that is reproducibly effective [27, 64, 65]. The excision may be done in stages, depending on the size of the plaque, and tightness of the scalp if primary closure is done. Healing by secondary intention is another option, and is preferred by some authors. Excision using the CO_2 laser with secondary intention healing may be an acceptable alternative, based on a small study [79].

11.5.2 Acne Necrotica

Synonyms
folliculitis necrotica

Key Features

- Adults affected.
- Pruritic or tender red to reddish-brown papules and papulopustules that develop central hemorrhagic crusts and leave varioliform scars.
- Frontal scalp and upper forehead characteristically involved.
- Chronic, relapsing course.
- Histopathology shows lymphocyte-mediated necrosis of the upper pilosebaceous unit in early disease variably associated with neutrophils in the dermis.

11.5.2.1 History

Acne necrotica was first described by Bazin in 1851 [11]. Hebra added the descriptor *varioliformis* based on the pock-like scars left in the wake of active disease [71]. Sabouraud, in 1928, and Lane in 1933 recognized a mild, nonscarring variant of the condition and dubbed it acne necrotica *miliaris* [95, 146].

11.5.2.2 Epidemiology

Acne necrotica is a rarely encountered condition that usually has its onset in adulthood [55, 89].

11.5.2.3 Pathogenesis

The etiopathogenesis of acne necrotica is unknown. *Propionibacterium acnes* or *Staphylococcus aureus* folliculitis, staphylococcus toxin, host hypersensitivity to folliculitis, excoriations of folliculitis, and a rosacea-like process have all been invoked [89, 107, 165]. The miliaris variant, which is nonscarring, is thought to represent a mild, early or abortive form of the disease. There is one case report of acne necrotica in which a drug, phenylbutazone, was clearly implicated [75].

11.5.2.4 Clinical Features

In acne necrotica *varioliformis*, the frontal scalp and adjacent forehead are typically affected [165] (Fig. 11.11). Other regions of the face and scalp, and the neck and trunk, in a seborrheic distribution, may also be involved. Crops of variably pruritic or tender, juicy 2- to 6-mm reddish-brown follicular papules and papulopustules arise and within days umbilicate and undergo central necrosis. *Staphylococcus aureus* and *Propionibacterium acnes* are the most common pathogens isolated from the pustules [55, 107]. Punched-out hemorrhagic crusts follow which are shed within a few weeks, leaving varioliform scars. A few lesions usually appear with each outbreak, but can number 100 or more. Aggravation in the summer has been reported [89] but in general the condition is chronic, with a waxing and waning course. Disfiguring, cribriform scarring can result in long-standing disease.

In contrast, acne necrotica *miliaris* is characterized by intensely pruritic, pinpoint vesicopustules on the scalp that are quickly excoriated, leaving angulated crusts [165]. Thus, primary disease is rarely seen at presentation. Hair regrowth is expected.



Fig. 11.11 Acne necrotica. Similar lesions are seen in the frontal scalp as well

11.5.2.5 Pathology

Early disease is marked by a superficial perifollicular and perivascular lymphocytic infiltrate with lymphocytic spongiosis and individual cell necrosis of keratinocytes in the upper outer root sheath [89]. Subepidermal edema is often prominent. Confluent necrosis of the upper pilosebaceous unit and adjacent epidermis follows. A fibrotic "zone" of destruction results, within which is contained shards of naked-hair-shaft foreign-body granulomas. Neutrophils are variably present, and can be seen in the dermis beneath a bacterial-laden stratum corneum or late in disease. Thus, acne necrotica might more aptly be classified as a lymphocytic subtype of primary cicatricial alopecia. Further study is needed for clarification.

11.5.2.6 Differential Diagnosis

In the words of Plewig and Kligman, "awareness of this bizarre disease is a prerequisite for an accurate diagnosis" [134]. Bacterial folliculitis, excoriations, eczema herpeticum, and molloscum contagiosa are in the differential. Care should be taken to inspect the affected area for the hallmark scars of prior episodes – a distinguishing feature seen in acne necrotica alone. The restricted involvement of the frontal hairline is also suggestive. Observation of individual lesions over time can also help to establish the diagnosis.

11.5.2.7 Treatment

Treatment of acne necrotica can be challenging. There is no consistently effective agent (Table 11.9). Antibiotics should be tried first. Intact pustules should be swabbed and cultured under aerobic and anaerobic conditions

Table 11.9 Evidence-based rating of treatment for acne necrotica varioliformis

Antibiotics, oral and topical	4
Topical and intralesional corticosteroids	5
Isotretinoin	5

to direct choice – usually an antistaphylococcal, or isotretinoin (1–2 mg/kg per day ×20 weeks) when *Propionibacterium acnes* is isolated. In the event no pathogen is identified, topical clindamycin, an oral antistaphylococcal, or tetracycline is recommended. Antibacterial soaps may be used adjunctively. With the exception of isotretinoin, which can induce a rapid response with prolonged remission [107], most agents produce only a transient benefit that can last from weeks to months, before relapse occurs [145]. In partial responders, further improvement may be gained with the addition of a topical corticosteroid or intralesional triamcinolone acetonide injections [89, 145]. In nonresponders otherwise treated, a trial of isotretinoin may be instituted (30 mg daily) for 1–2 months, and abandoned thereafter if ineffective. In the authors' and others' experience, topical retinoids are ineffective [134]. Although of unproven benefit, treatment of bacterial carriage sites with mupirocin ointment periodically should be considered where applicable.

11.5.3 Erosive Pustular Dermatosis

Synonyms
erosive pustular dermatosis of the scalp

Key Features

- Elderly onset.
- Moist erosion or boggy, crusted plaque, often at site of former trauma.
- Histopathology nonspecific and not clearly folliculocentric.
- Categorization as primary or secondary cicatricial alopecia indeterminate.

11.5.3.1 History

The first case of erosive pustular dermatosis of the scalp was reported in 1977 by Burton [26]. A 78-year-old female presented with an "irritable, red, scaly" area on the vertex that became studded with sterile pustules and subsequently formed a large crusted "boggy mass." Only when a potent topical corticosteroid was instituted did the condition abate.

11.5.3.2 Epidemiology

This is a rarely encountered condition that largely affects the elderly, with a mean age of 75 at the time of presentation according to one report [68, 141, 145]. Case reports have originated from Europe, the United States, and Japan. There is no clear sex predilection. There are no reported cases in blacks.

11.5.3.3 Pathogenesis

The cause of erosive pustular dermatosis of the scalp is not known, however there are some intriguing clues. Most cases can be related to prior trauma to the site, either accidental or iatrogenic [68, 145]. Examples include herpes zoster, surgery or X-ray therapy for squamous or basal cell carcinoma, and cryotherapy, topical fluorouracil or retinoids for actinic keratoses. Chronic sun damage, which would explain the predominance of this entity in elderly non-blacks and the frequent occurrence in bald scalp, is thought to be a predisposing factor [68].

It remains to be determined if erosive pustular dermatosis is a primary or secondary form of cicatricial alopecia, as the features of early disease have not been characterized and a folliculocentric process has not been consistently observed.

11.5.3.4 Clinical Features

Patients complain of a nonhealing, crusted, weeping wound on the scalp, which they may relate to antecedent trauma to the site. Onset can predate the trauma by months to years [68, 141, 145]. Symptoms are usually absent. All sites of the scalp can be affected. Examination typically reveals a spongy, superficially crusted plaque devoid of hair. Beneath the crust, which can be easily detached, a glistening red erosion with "lakes of pus" [26] or numerous flaccid pustules is seen. Occasionally only a moist erosion is seen. Untreated disease undergoes episodic pustular flares, with gradually enlargement over years [26, 141]. With treatment, hair regrowth may occur but often an atrophic scarred plaque results. Wound cultures are occasionally positive – usually for *Staphylococcus* or *Candida* species – but probably reflect secondary colonization [68, 141]. Care should be taken to avoid attempts to surgically repair

the wound and treatment of surrounding actinic keratoses as extension of disease can result, presumably due to the Koebner phenomenon. There is an isolated report of secondary carcinoma developing in long-standing disease [102].

11.5.3.5 Pathology

Primary involvement of the hair follicle has not been clearly demonstrated on histopathology [68, 141]. However, characterization of early disease is lacking. Overall, the findings are nonspecific. Depending on the site of biopsy the epidermis is normal, parakeratotic, acanthotic, atrophic or eroded. Subepidermal neutrophils are occasionally seen. In the dermis, a focal or diffuse, chronic lymphoplasmacytic infiltrate is present. Naked hair-shaft granulomas are often interspersed. Pilosebaceous units are reduced in number or absent with remnant arrector pili. Direct immunofluorescence is negative.

11.5.3.6 Differential Diagnosis

There is a wide differential for erosive pustular dermatosis. Infectious causes must be eliminated, namely bacterial pyoderma, kerion, and erosive candidiasis. Noninfectious mimickers in the elderly include pyoderma gangrenosum, cicatricial pemphigoid, pemphigus vulgaris, pustular psoriasis, ulcerative lichen planus, temporal arteritis, and blastomycosis-like pyoderma. A recently described entity – amicrobial pustulosis associated with autoimmune disease – has scalp features reminiscent of erosive pustular dermatosis, but is accompanied by an intertriginous pustular eruption and is typically seen in young women with autoimmune disease.

11.5.3.7 Treatment (Table 11.10)

First-line therapy is a potent topical corticosteroid [68, 141, 145]. Improvement usually begins within days, with complete resolution within a few weeks. Relapse with cessation is common; gradual titration to the lowest dosing schedule is recommended for maintenance.

Table 11.10 Evidence-based rating of treatments for erosive pustular dermatosis

Potent topical corticosteroids	4
Topical calcipotriol	5
Topical tacrolimus	5

In nonresponders or those who have significant atrophy secondarily, topical calcipotriol cream may be tried [15]. In an isolated treatment-refractory case, disease-free remission with hair regrowth was induced after twice-daily use for 2 months. A third, effective option is 0.1% topical tacrolimus, used once to twice daily [93, 147]. Conflicting results have been reported with oral zinc sulfate, isotretinoin, and nimesulide [93, 108, 145]. Dapsone and sulfapyridine appear to be ineffective based on limited data [93, 145]. Topical retinoids and corrective surgery should be avoided, as these can exacerbate disease.

11.6 Surgical Correction of Burnt-Out Cicatricial Alopecia

In patients who have cosmetically bothersome, burnt-out disease – which may be defined as asymptomatic, clinically inactive, stable hair loss for 2 years – hair transplantation and/or scalp reduction is an option. The choice of the surgical approach is best done by the surgeon who will explain the pros and cons of the procedure to the patient. It is important to inform the patient of the risks. Hair is a target of disease and moving it into a "nonactive" area could potentially result in recrudescence. Thus, it may be advisable to do a test area first. Moreover, in conditions that can koebnerize (e.g., discoid lupus erythematosus) prophylaxis with an appropriate medication is advised in the perioperative period.

11.7 General Measures for Management of Cicatricial Alopecia

In addition to disease-specific treatments, several measures apply to management of all forms of cicatricial alopecia. First, in sun-exposed areas of scarring, patients should be instructed to apply broad-spectrum sunscreen and to wear a tightly woven hat when outdoors. Second, treatment with topical 2%–5% minoxidil twice daily may be instituted to help thicken hairs in those with coexisting androgenetic alopecia, and to potentially prolong the anagen phase in others [145]. Benefit should be evident within 6–12 months. Third, methods of cosmetic camouflage should be discussed to help ease the discomfort or embarrassment that some patients feel who have lost their hair. These include: (1) use of partial or complete hairpieces; (2) tinted cosmetic creams and keratin fibers that match the hair color; (3) highlighting darker hair with tones that more closely match scalp skin color so as to reduce the color contrast; and (4) alternative coiffures. Significant restoration of self-esteem and

confidence can result from all these measures. Finally, patients should be referred to the North American Hair Research Society (www.nahrs.org) and the Cicatricial Alopecia Research Foundation (CARF; www.carfintl.org) websites, both excellent resources for individuals with primary cicatricial alopecia to learn more about their disease, research efforts, and upcoming patient-focused and scientific meetings on the subject.

Summary for the Clinician

The primary cicatricial alopecias are an intriguing, varied group of disorders that likely have a diverse, multifactorial origin. Early recognition and aggressive treatment of active disease is of paramount importance to thwart further hair loss. Although the choice of treatment is not bolstered by controlled, blinded studies in most cases, a tiered approach using evidence-based outcomes, drug side-effect profile and individual aspects of disease (extent, severity, symptoms, age and patient preference) will guide management. Combination therapies may be warranted in partial responders. With the advent of newer bench-based technologies such as gene mapping, novel therapies such as the immune response modifiers, and a collective effort among researchers and clinicians alike to further the bounds of knowledge on the subject, one can anticipate further gains in the understanding and management of these conditions in the not too distant future.

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Chapter 12

Secondary Cicatricial and other Permanent Alopecias

12

Andreas M. Finner, Jerry Shapiro

Synonyms

secondary scarring alopecia, secondary fibrosing alopecia

Key Features

- Various non-follicular scalp conditions can cause secondary scarring or permanent alopecia.
- Possible causes are congenital defects, trauma, inflammatory conditions, infections, neoplasms, and, rarely, drugs.
- Associated signs and symptoms and other diagnostic procedures may aid in the diagnosis.
- Detection of the underlying disorder may be difficult in end-stage lesions.
- Treatment is specific in active conditions; surgery is an option in localized scars.

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12.1 Introduction

Permanent hair loss can be caused by various scalp conditions when hair follicles are destroyed as an "innocent bystander." In these conditions, the primary event develops outside the follicular unit and this leads to incidental destruction of the follicle. They have been termed secondary cicatricial alopecias [90]. The term secondary cicatricial alopecia may be inaccurate, because only some of these conditions cause true scarring or fibrosis [98, 127]. Some of these conditions involve destruction of the pilosebaceous unit by a non-fibrotic mechanism. Displacement of the follicle by other infiltrating cells (displacement alopecia) can occur. The process may also involve interstitial elastic tissue deposition and hyalinization of pre-existing collagen (pseudocicatricial alopecias). It may, therefore, be more appropriate to use the term secondary permanent alopecias for this group of hair loss disorders. The term atrophizing alopecias was also proposed [134].

Diagnosis in early stages can sometimes be made based on specific clinical and histologic features of the underlying disorder. In the end-stage, many true scar-

Table 12.1 Secondary cicatricial (permanent) alopecias, a classification based on etiology *(see next page)*

Secondary cicatricial (permanent) alopecias	
1. Genodermatoses and developmental defects with permanent alopecia (excluding congenital hypotrichoses and atrichias)	Ectodermal dysplasias
	Aplasia cutis congenita
	Incontinentia pigmenti
	Porokeratosis mibelli
	Ichthyosis
	Hereditary epidermolysis bullosa
	Meningocele
	Hamartoma
	Organoid nevi (sebaceous, epidermal)
	Vascular malformations
	Darier's disease
	Fibrodysplasia
2. Physical and chemical injury	Mechanical trauma and pressure
True cicatricial	Scratching
	Burns
	Freezing
	Chemical injury
	Insect bites
Pseudo-cicatricial	Radiation
3. Infections	
True cicatricial	*Bacterial*
	Leprosy
	Tertiary syphilis
	Tuberculosis-lupus vulgaris
	Viral
	Zoster
	Varicella
	Tinea capitis
	Kerion
	Favus
	Protozoic
	Leishmania
4. Inflammatory dermatoses	
Pseudo-cicatricial	Psoriasis (rarely)
	Pityriasis amiantacea
	Arteriitis temporalis
4. Inflammatory dermatoses	
Pseudo-cicatricial	Pyoderma gangraenosum
	Graft-versus-host disease
	Sclerosing
	Morphea
	Scleroderma en coup de sabre and Parry-Romberg syndrome
	Lichen sclerosus et atrophicus
	Bullous
	Cicatricial pemphigoid
	Porphyria cutanea tarda
	Acquired Epidermolysis Bullosa
Displacement	*Granulomatous*
	Sarcoidosis
	Granuloma anulare
	Necrobiosis lipoidica (including Miescher's granulomatosis)
5. Drugs	
6. Neoplasms	
Displacement	*Infiltration*
	Lymphoproliferative disorders
	Mastocytosis
	Benign solid neoplasms
	Cysts
	Vascular tumors
	Adnexal tumors
	Plasmocytoma
	Malignant solid tumors
	Angiosarcoma
	Dermatofibroscarcoma protuberans
	Malignant fibrous histiocytoma
	Melanoma
	Squamous cell carcinoma
	Basal cell carcinoma
	Metastasis (alopecia neoplastica)
	Lymphoma

ring alopecias show no specific changes. Follicular orifices are lost clinically and histology shows extensive scarring with fibrosis, and loss of elastic fibers and adnexal structures. This non-specific end-stage has also been termed Pseudopelade of Degos [26]. It should not be confused with Pseudopelade of Brocq, which is controversially discussed and may represent a distinct entity.

When the outcome of permanent hair loss is the basis of classification, more conditions fall into this category, such as some typically non-scarring, reversible alopecias that can become de facto permanent when they persist for longer time periods. Whether these conditions are simply chronic because no appropriate treatment is yet available or become definitely irreversible at some point is unclear. A "follicular dropout" was postulated in these conditions. They have been termed "transitional alopecias" [127] "biphasic alopecias" [122] or "permanent alopecias due to a persistent disturbance of the hair cycle" [134]. Examples are chronic longstanding alopecia areata and androgenetic alopecia. In the latter condition, an inflammation and small scars have been found in some follicles. Senescent alopecia, an incompletely characterized concept, is another condition with permanent, diffuse hair loss. Permanent, chronic traction alopecia [53] is considered to be part of this group as well. Scarring was seen in some chronic stages [142]. Similar phenomena may occur in repeated plucking of unwanted hair.

The pathogenesis of many of the underlying conditions as well as the concept of scarring alopecia itself remains incompletely understood. Destruction of stem cells located in the bulge is thought to be the underlying process, but disturbance of the anagen bulb including the papilla and sebaceous gland function may also be involved. One of the unanswered questions is how a mesenchymal process such as scarring and hyalinization can cause destruction of epithelial hair follicle cells [54]. New insights, especially with advancements in molecular biology, will lead to a better understanding and new classification of this group of alopecias.

A list of conditions that can cause secondary cicatricial and other permanent alopecias is given in Table 12.1. Some of the more common or clinically relevant conditions are discussed in this chapter (Table 12.1).

12.2 Genodermatoses and Developmental Defects with Alopecia

This includes loss of hair after birth. Congenital hypotrichoses, atrichias, and temporal triangular alopecia are discussed in Chaps. 14 and 16. Hypotrichosis Marie-Unna, where permanent alopecia develops later in life, is discussed in Chap. 14.

12.2.1 Ectodermal Dysplasias

Scalp dermatitis is a feature of several ectodermal dysplasias with clefting and can lead to scarring [40]. An erosive dermatitis of the centroparietal scalp in the first months of life is part of ectrodactyly-ectodermal dysplasia-clefting (EEC) syndrome and can lead to cicatricial alopecia [133]. The course is chronic. Therapy should be directed at prevention of infection and trauma. Ectodermal dysplasias are divided into groups A and B in the Freire-Maia classification. These conditions are discussed in detail in Chap. 14. A case of Rapp–Hodgkin's syndrome with cicatricial alopecia has recently been described [94].

12.2.2 Aplasia Cutis Congenita

Synonyms
congenital absence of skin, congenital scars

Key Features

- Localized areas of skin are absent or scarred at birth.
- Endpoint of various events leading to defects in skin formation.
- The scalp is most commonly affected.
- Underlying embryologic malformations may be present.
- May be associated with abnormalities or be part of a syndrome.

12.2.2.1 Introduction

Aplasia cutis congentia (ACC) is a localized congenital absence of epidermis and dermis, often including the subcutis. It represents a physical finding that may result from many different intrauterine events disrupting skin development. Some 60%–85% of cases are localized on the scalp, mostly in the midline. The skull is affected in 20%–30% of these cases. Larger, irregular lesions may also involve the dura and leptomeninges. Dilated scalp veins may also be present. There is a single ACC lesion in 70% of cases.

12.2.2.2 History

The condition was first described by Cordon in 1767.

12.2.2.3 Epidemiology

The incidence in newborns is estimated at 1:3000. There are forms with autosomal-dominant and autosomal-recessive inheritance, while others occur sporadically.

12.2.2.4 Pathogenesis

The etiology is heterogeneous and still debated. A classification distinguished nine groups based on the number and location of lesions and the absence or presence of associated defects [43]. Possible causes for aplasia cutis include defective neural tube closure during embryogenesis, intrauterine trauma, tensile forces during brain development, and vascular occlusion with skin necrosis. Somatic mutations are thought to be the cause for other cases. Methimazole and other teratogens such as misoprostol and valproic acid have been implicated in the development of this condition when given to women during pregnancy. Other cases have been reported following intrauterine varicella zoster or herpes simplex viral infections. Aplasia cutis congenita can be a symptom of several syndromes, such as Trisomy 13.

12.2.2.5 Clinical Features

In most cases, there is a sharply circumscribed, single lesion of 0.5–10 cm diameter. It initially presents as an ulcer over the vertex near the whorl or near the sagittal suture with an erythematous base. Other lesions present as membranous ACC with a parchment-like surface or have a stellate appearance, which is thought to indicate a vascular etiology. The defect is then covered by skin or granulomatous tissue, spontaneously healing with scarring in the following months. Keloid formation is possible. In newborns, the ulceration can lead to hemorrhage such as life-threatening sagittal sinus hemorrhage, thrombosis, infection, and meningitis. Sometimes, children are already born with scarred lesions. Associated ectodermal dysplasias and malformations have to be ruled out (Fig. 12.1).

12.2.2.6 Pathology

Biopsies are most often performed later in childhood. The epidermal rete ridges are typically flattened. Dermal thickening with decreased elastic fibers and loss of follicles and other adnexal structures can be seen. In the center of the lesion, thickened sclerotic and parallel collagen bundles have also replaced superficial parts of the subcutaneous fat. There is no inflammation in healed lesions.

12.2.2.7 Differential Diagnosis

Conditions that may present with similar features include birth trauma and neuroectodermal defects (encephaloceles, heterotropic brain tissue). The latter may be surrounded by a collar of hypertrophic hair ("hair collar sign") and an underlying cranial defect should be radiologically excluded. A blistering disease should also be excluded.

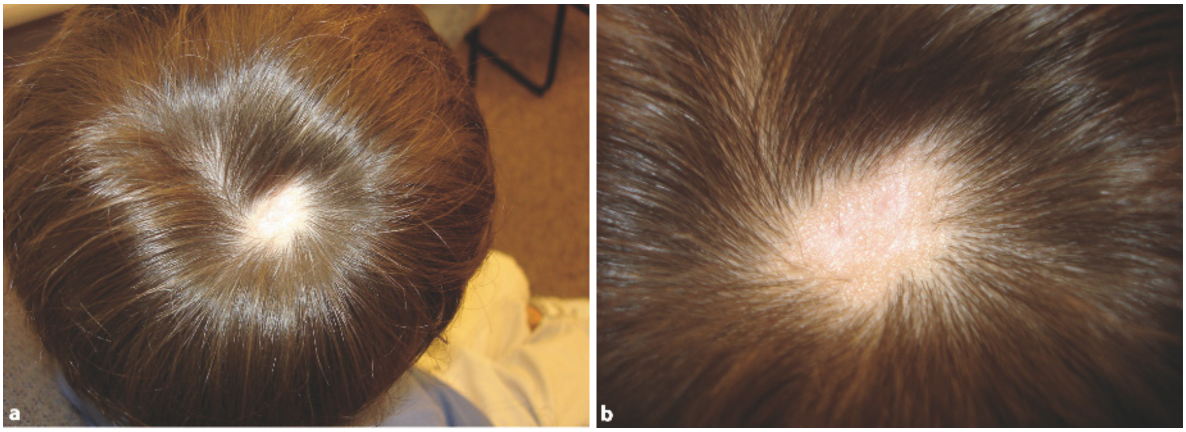


Fig. 12.1a,b A sharply circumscribed patch of alopecia in aplasia cutis

12.2.2.8 Treatment

Usually, management of the healing lesions is symptomatic. Surgical correction can be necessary, especially for large and multiple defects, in cases with a dural defect or when the sagittal sinus is affected. Especially in larger lesions or before surgery, imaging studies should be performed to visualize underlying structures. If primary closure is not feasible, the use of tissue expanders and rotation of a flap to fill the defect or skin and bone grafts may be required. Engineered skin may be another treatment option. In most cases, the scarred lesion is completely excised at an older age and/or treated with hair transplantation.

12.2.3 Incontinentia Pigmenti

Synonyms
Bloch-Sulzberger's syndrome

Key Features

- Almost only girls are affected.
- The condition presents in three stages along the lines of Blaschko.
- Irregular scarred patches in a whorled pattern are found after scalp involvement.
- Associated malformations can occur.

12.2.3.1 Introduction

This X-linked dominant neurocutaneous syndrome can affect the scalp in 25% of cases and then results in cicatricial alopecia, often showing a whorled pattern [27].

12.2.3.2 History

The condition was first described by Bloch in 1926 and Sulzberger in 1927.

12.2.3.3 Epidemiology

This is a very rare condition, affecting females in more than 95% of cases. Several hundred cases have been reported in the literature: 28% of patients have a positive maternal family history, in 62% there is sporadic mutation. In more than 80% of sporadic cases, germline mutations in the father have been reported.

12.2.3.4 Pathogenesis

There is a mutation in the NEMO/IKK-gamma gene on chromosome Xq28, in 80% a single mutation with deletion of exons 4–10. It is lethal for the male fetus. Improper gene function results in inhibition of NFκB and increased susceptibility to apoptosis (blistering stage) and consecutive proliferation of remaining IKK-active cells (verrucous stage) [116]. The mutated cells are thus destroyed and replaced by non-affected cells. In affected females, a functional mosaic is formed by X-chromosomal inactivation (Lyon effect). Incontinentia pigmenti can occur in males with Klinefelter syndrome (XXY syndrome) or with somatic mosaicism or hypomorphic (less deleterious) mutations.

12.2.3.5 Clinical Features

The disorder presents in three clinical stages and starts in early infancy or even in utero. Initial blisters in a characteristic distribution along the lines of Blaschko develop into lichenoid, verrucous papules after several months. They finally result in linear, whorled hyperpigmented atrophic lesions, which may slowly fade or even become hypopigmented. While the legs are usually most severely affected, scalp lesions can lead to central or linear scarred alopecic patches with a bizarre polycyclic pattern. An association with aplasia cutis is seen in Goltz–Gorlin syndrome. In the initial stages, eosinophilia is present. Associated malformations of the teeth (80%), nails (7%–40%), eyes (20%–35%), central nervous system (CNS) (30%), skeleton, heart, and vessels can occur.

12.2.3.6 Treatment

Management of active lesions is symptomatic to prevent superinfection. Associated malformations require specific treatment. Genetic counseling should be offered. Few centers offer genetic testing of the mutation. Mothers with incontinentia pigmenti have an equal chance of having a normal or affected daughter or a normal son. Alopecic patches can be surgically removed or filled in with autologous follicular unit grafts (Fig. 12.2).



Fig. 12.2 Scarring alopecia in Incontinentia pigmenti Bloch Sulzberger

12.2.4 Ichthyosis

Synonyms
alopecia ichthyotica

Key Features

- Large heterogeneous group of disorders of cornification.
- Scaling of skin is present.
- Superinfection may cause chronic folliculitis.
- Therapy is symptomatic, many patients also respond to oral retinoids.
- Scarring alopecia was reported in congenital ichthyosiform erythroderma (OMIM #242100), lamellar (OMIM #242300) and X-linked ichthyosis (OMIM #308100).

12.2.4.1 Introduction

This is a heterogeneous group of primary and secondary scaling disorders, caused by mutations in keratins or proteins involved in cornification. The autosomal-recessive forms of non-bullous congenital ichthyosiform erythroderma (NCIE) and lamellar ichthyosis (LI) were reported to cause large areas of cicatricial alopecia [5, 71, 123, 131], as well as the X-linked recessive form (XLI) [144]. In infantile types, such as the collodion baby and harlequin fetus, cicatricial alopecia results if the baby survives.

KID syndrome, which is characterized by keratitis, ichthyosis and deafness, can be accompanied by a folliculitis leading to scarring alopecia.

12.2.4.2 Epidemiology

The incidence is reported for CIE at 1:100,000–1:200,000; LI, at 1:300,000; and for XLI, 1:2000–1:6000 in males. Scalp involvement and cicatricial alopecia are rare.

12.2.4.3 Pathogenesis

In NCIE and LI, different defects lead to a higher epidermal turnover with consecutive proliferation hyperkeratosis. In XLI, there is retention hyperkeratosis with delayed dissolution of desmosomes in the stratum corneum due to steroid sulfatase and arylsulfatase C deficiency. The exact underlying mechanisms of ichthyotic alopecia are not fully understood. Inflammation, fibrosing processes, and folliculitis lead to permanent alopecia.

12.2.4.4 Clinical Features

Congenital ichthyosiform erythroderma and LI are inflammatory and lead to loss of follicles. Bacterial and fungal superinfection is common and can cause folliculitis. In X-linked ichthyosis, lesions begin on the scalp and later affect other areas. Fish-scale-like hyperkeratosis develops in the first days of life. Corneal abnormalities, cryptorchism, and uterine inertia may be associated (Fig. 12.3a–c).

12.2.4.5 Treatment

Topical keratolytic agents such as salicylic acid should be combined with antiseptic preparations. Emollients containing lactic acid or urea are important in symptomatic management. Topical vitamin A and tazarotene are also used. Topical *N*-acetylcysteine has an antiproliferative effect. Systemic retinoids have been shown to be effective but require long-term or interval treatment. They can cause diffuse telogen effluvium and other side-effects and should be reserved for severe cases. A scalp

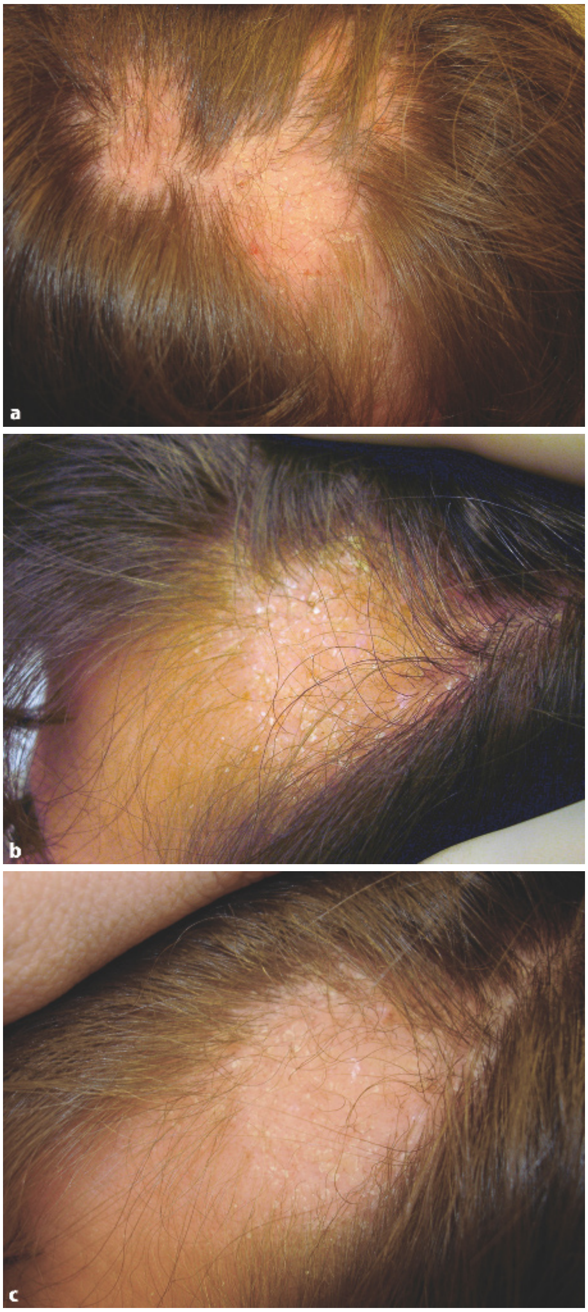


Fig. 12.3a–c Permanent alopecia in ichthyosis: epidermolytic hyperkeratosis

prosthesis (hairpiece) may become necessary for larger scarred areas.

12.2.5 X-Chromosomal Chondrodysplasia Punctata

Synonyms
Conradi's syndrome (1917), Conradi-Huenermann's syndrome (1931), Happle's syndrome (1979) (OMIM 302960)

Key Features

- Bone and other abnormalities are accompanied by ichthyosiform skin lesions in 25%.
- These lesions can cause cicatricial alopecia.

This is a special type of ichthyosis. In the X-linked dominant variant, there are not only bone abnormalities but also an ichthyosiform erythroderma or localized lesions that potentially cause atrophoderma and cicatricial alopecia [33]. There is a defect on gene Xp11.22-p11.23, encoding for emopamil-binding protein (sterol-Δ8-Δ7-isomerase), which is crucial in cholesterol metabolism.

12.2.6 Hereditary Epidermolysis Bullosa (EB)

Synonyms
junctional EB [subtype Herlitz (OMIM #226700)], dystrophic EB [subtype Hallopeau-Siemens (OMIM #226600)]

Key Features

- Hereditary disorders characterized by fragile skin leading to blister formation.
- Three major groups differing in the level of blister formation: simplex (epidermolyic), junctional, and dystrophic (dermolytic).
- Cicatricial alopecia reported in junctional and dystrophic EB.
- More severe forms can affect other organs.
- Specific therapy is not available; management is directed at prevention of blister formation and complications.

12.2.6.1 Introduction

This is a group of hereditary disorders characterized by easy blistering caused by mechanical forces with underlying defects in structural proteins. They are divided into intraepidermal (EB simplex), junctional (JEB), and dermolytic (DEB) types [38]. The scarring forms of Herlitz (JEB), Hallopeau-Siemens (DEB) and generalized atrophic benign EB (DEB) have been reported to result in permanent alopecia [28, 51, 55, 141]. Scalp involvement and patchy alopecia are especially frequent in dystrophic epidermolysis bullosa.

12.2.6.2 Epidemiology

The overall incidence of EB has been estimated at 1:20,000 to 1:100,000. Girls and boys are equally affected.

12.2.6.3 Pathogenesis

In the Herlitz type (autosomal-recessive epidermolysis bullosa atrophicans generalisata gravis), there is junctional blister formation due to mutations in the genes LAMB3, LAMC2 and LAMA3 encoding for laminin 5, which is an anchoring filament between the lamina densa and hemidesmosome.

The Hallopeau-Siemens type (recessive dystrophic epidermolysis bullosa) and other forms of DEB are dermolytic caused by a defect or absence of collagen type VII, which is an important part of anchoring fibrils between the lamina densa and papillary dermis. This is due to mutations in the COL7A1 gene on 3p21.3. An increased synthesis of abnormal collagenase VII has also been observed.

12.2.6.4 Clinical Features

Clinically, the subepidermal vesicles show little inflammation. Erosions and ulcers develop. Nail dystrophy, milia, scars with contraction deformities and mutilations, and permanent alopecia are frequent in these severe types.

12.2.6.5 Pathology

On histologic examination, there is extensive clefting between follicular epithelium and dermal adventitia extending deep down along the follicle [127].

12.2.6.6 Differential Diagnosis

Epidermolysis bullosa acquisita due to antibodies directed against procollagen VII can also lead to permanent alopecia. While DADPS (dapsone) is used in children, the standard treatment consists of glucocorticoids and ciclosporin.

12.2.6.7 Treatment

There is no causal therapy. Management involves supportive care to prevent trauma, contraction, malnutrition, and superinfection. Gene therapy would be a possible approach. Esophagus stricture and squamous cell carcinoma (SCC) can develop as major complication.

12.2.7 Porokeratosis of Mibelli

Synonyms
parakeratosis Mibelli (OMIM #175800)

Key Features

- An acquired or hereditary clonal keratinization anomaly with parakeratotic lesions.
- The cornoid lamella is a specific histologic sign.
- Scalp involvement can cause cicatricial alopecia.
- Four other clinical variants of porokeratosis are known.

Very rare cases of cicatricial alopecia following this autosomal-dominant or sporadic keratinization anomaly have been reported. Classic PM is twice as common in men than in women. One or more expanding erythematous, keratotic plaques of several millimeters to centimeters size with elevated ridge-like edges and central atrophy are formed. The ridge typically exhibits a thin central furrow. The parakeratosis probably disrupts the hair follicle structure and effectively destroys it. There is a risk of carcinoma developing in these lesions, probably due to chromosome instability or decreased immune surveillance with p53 over-expression. Acquired superficial disseminated actinic porokeratosis may cause cicatricial alopecia too.

12.2.8 Meningoceles

Neural tube defects such as rudimentary meningoceles and encephaloceles can present as a pink nodule or patch of alopecia, sometimes annular. A capillary stain or a tuft or collar of hair has also been reported. They are usually localized in the midline and recognized at birth. Before performing surgery in infants, especially in midline alopecic patches, an intracranial connection has to be excluded by imaging studies [103, 124].

12.2.9 Generalized Hamartoma

Occult eccrine sweat duct hamartoma was reported to result in cicatricial scalp alopecia [132]. There have also been cases of follicular hamartoma and alopecia [74, 79] and basaloid cell hamartoma [3]. The hair follicles undergo abnormal growth and do not support hair fiber formation. Biopsy tests reveal the presence of empty follicles and follicular cysts. Congenital dermoid cysts were reported to result in focal scarring alopecia [115].

12.2.10 True Epidermal and Organoid Epidermal Nevi

Synonyms
epithelial nevus, nevus sebaceous of Jadassohn

Key Features

- Organoid epidermal nevi are hamartomas with an imbalance of skin structures and impaired hair development.
- In nevus sebaceous, sebaceous glands prevail presenting as yellow grouped papules present from childhood, preferably on the scalp.

Key Features

- It can be associated with other abnormalities and develop into adenomas or basal cell carcinoma.
- True epidermal nevi only occasionally affect the scalp.

12.2.10.1 Introduction

Organoid epidermal nevi result from an imbalance in adnexal structures due to a localized somatic mutation (complex hamartoma). If sebaceous glands predominate, *sebaceous nevi* are formed, often along the lines of Blaschko. They are usually localized on the scalp and result in permanent alopecia with incomplete follicle development.

In contrast, true epidermal nevi represent epithelial changes and alopecia only occasionally occurs. While these epidermal nevi can be a symptom of specific syndromes, a linear nevus sebaceous can be part of Schimmelpenning–Feuerstein–Mims syndrome (syndrome of the linear nevus sebaceous, Jadassohn nevus phacomatosis, OMIM 163200) with associated abnormalities of the eyes, heart, and CNS.

12.2.10.2 Epidemiology

The incidence has been estimated at 1–3/1000. Males and females are equally affected.

12.2.10.3 Pathogenesis

Genetic mosaicism is thought to be the underlying cause, i.e., postzygotic somatic mutation. This also explains the common systematic appearance. The mutation affects pluripotential cells giving rise to hamartomas of different cell lines.

12.2.10.4 Clinical Features

In nevus sebaceous, grey or yellow-orange papules with a waxy appearance are grouped in a linear fashion. On palpation, they are soft and elastic. Face and scalp are commonly affected at birth. The lesion is raised at infancy, probably due to maternal hormones. It is less prominent in childhood and becomes verrucous and nodular after puberty, probably due to hormonal influences.

Benign trichoblastomas often develop within the nevus. There is a risk of syringocystadenoma papilliferum (8.6%), other types of appendageal tumors and basal cell carcinoma (BCC) (0.5%). This may be due to mutations in the patched gene, which has been found in nevus sebaceous. The incidence of BCC has been overestimated because of misinterpretation of areas of basaloid proliferation.

In epidermal nevi, hyperplasia leads to formation of papules mostly in a linear distribution. Specific types are

nevus verrucosus, soft epidermal nevus, epidermolytic epidermal nevus, and others. The latter form represents a localized form of epidermolytic hyperkeratosis due to a defect in keratin I or X. If there is also a gonadal mutation, there is a risk of having children with generalized epidermolytic hyperkeratosis (Fig. 12.4a,b).

12.2.10.5 Pathology

In nevus sebaceous of children, numerous but hypoplastic hairless sebaceous follicles are found. Mature hyperplastic sebaceous glands are formed with puberty. The hair follicles remain small and incapable of producing terminal hairs. In verrucous epidermal nevi, acanthosis, papillomatosis and hyperkeratosis with formation of pseudo horn cysts can be seen.

12.2.10.6 Differential Diagnosis

In childhood, the differential includes aplasia cutis, congenital triangular alopecia, juvenile xanthogranuloma and solitary mastocytoma. Later, a papillomatous melanocytic nevus or seborrheic keratosis may present with similar features.

12.2.10.7 Treatment

Despite the relatively low risk of malignant transformation in a nevus sebaceous, surgical excision, preferably before puberty, is still recommended but not mandatory if there is no hint of these conditions, such as rapid enlargement, ulceration or formation of a nodule [21]. However, many patients ask for removal for cosmetic reasons. True epidermal nevi can also be excised. Recurrence is frequent in other treatment modalities (ablative laser, cryosurgery, dermabrasion).

12.2.11 Vascular Malformations

Cavernous hemangioma can cause localized alopecia. This condition is discussed in Chap. 18.

12.2.12 Dyskeratosis Follicularis

> **Synonyms**
> Darier disease, Darier's disease (OMIM 124200), Darier-White disease

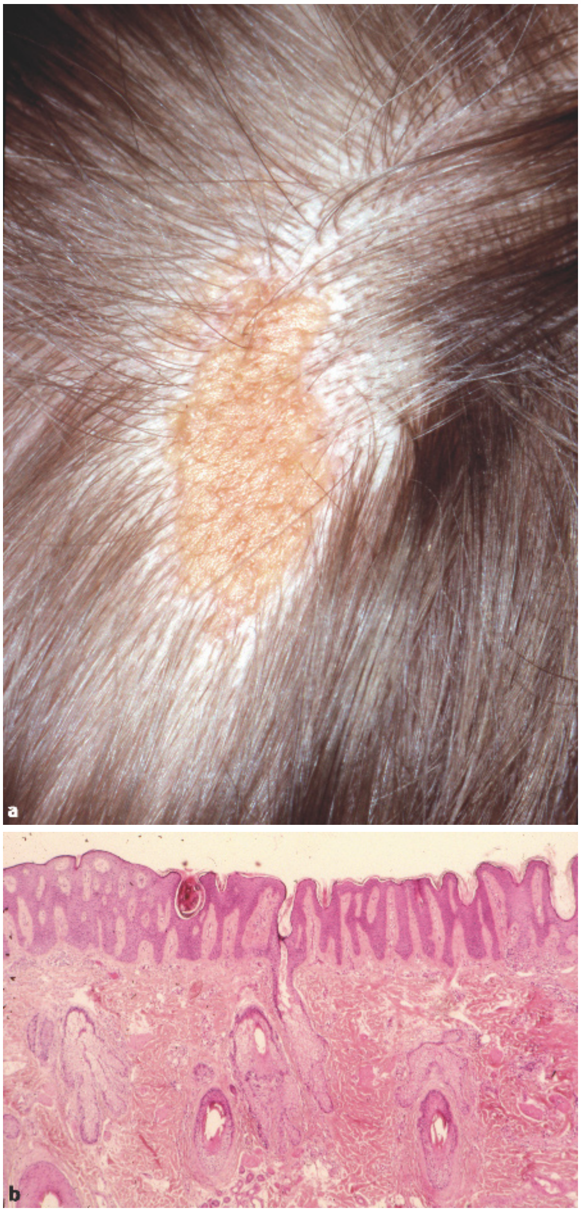


Fig. 12.4a,b Nevus sebaceous. Histology in adults shows a verrucous epidermis and large sebaceous glands

Darier disease (DD) is an autosomal-dominant chronic cornification disorder with premature cornification of single keratinocytes and acantholysis. There have been single reports of a cicatricial alopecia [84]. Brownish, rough, spinulous, follicular keratotic papules of 1–2 mm in size typically start in teenage years. They may be itchy, mainly affect the seborrheic areas and sometimes appear on the scalp, forehead, and retroauricularly.

12.2.13 Fibrodysplasias

Localized permanent alopecia of the scalp has been reported in the rare autosomal-dominant condition polyostotic fibrous dysplasia or Albright's disease [113]. Generalized loss of scalp hair is a frequent feature of the autosomal-dominant condition fibrodysplasia ossificans progressiva, occurring in 24% of cases [20].

12.3 Physical and Chemical Injury

12.3.1 Mechanical Trauma

Synonyms

pressure-induced alopecia, traumatic alopecia, post-labor alopecia, post-operative alopecia

Key Features

- Mechanical trauma can lead to permanent hair loss.
- Common causes include birth trauma, pressure-induced alopecia and traction alopecia.
- Specific locations and a careful history may aid in the diagnosis.

12.3.1.1 Introduction

Besides prolonged traction (mentioned above), the most common form of mechanically induced cicatricial alopecia results from *scalp injuries* (Fig. 12.5), such as accidents and machinery with pulling of hair and laceration, sometimes leading to descalpation.

Cicatricial alopecia has been reported as a result of *birth trauma* from intrauterine pressure [76], protracted labor or from forceps or vacuum extractors [108].

Long-lasting operations (especially with anesthesia for more than 24 h) or unconscious states without change in position (intubation, coma, influence of drugs, intoxication, suicide attempts) are reported to cause cicatricial alopecia [143]. This *pressure-induced alopecia* was also reported in newborns treated in the intensive care unit for hypoxemia and impaired cardiovascular function, resulting in ulcers and cicatricial alopecia of the occipital scalp [46]. More frequently, this alopecia is only temporary.

Prolonged pressure in women carrying baskets was also observed to cause permanent alopecia, as well as from wearing a head strap.

12.3.1.2 Epidemiology

The incidence of permanent alopecia from birth trauma has been reported at 0.3% [15] and 1% [10].

12.3.1.3 Pathogenesis

Alopecia from birth trauma sometimes occurs with preceding contusions, hematoma, caput succedaneum, and bacterial infections of traumatized areas. Pressure-induced alopecia results from ischemia. Factors such as anemia, vasoconstrictive drugs (vasopressin), and hypoxemia may also contribute.

12.3.1.4 Clinical Features

In postoperative pressure-induced alopecia, tenderness, swelling, erythema, and also exudation are typical in the initial stages. Hair loss occurs 1–4 weeks after the event. If scarring has occurred, the lesion usually presents as an oval hairless patch on the occipital scalp.

12.3.1.5 Pathology

In early pressure-induced alopecia, vascular thrombosis, inflammation, and destruction can be seen in the dermis. In non-permanent cases, synchronous conversion into catagen and anagen, trichomalacia, and pigment casts in the collapsed root sheaths are found. Dermal fibrosis as well as vascular, tissue and fat necrosis with foamy macrophages surrounded by mild inflammation develop after irreversible damage [52].



Fig. 12.5 Self-inflicted, artificial mechanically induced scarring alopecia in a 10-year-old girl

12.3.1.6 Prophylaxis

Frequent intra- and postoperative repositioning of the head can prevent pressure-induced alopecia.

12.3.2 Burns

Synonyms
post-burn alopecia

12.3.2.1 Introduction

Third degree burn can lead to scarring alopecia. Usually other body parts are affected as well [18]. Temperatures above 60°C can lead to third-degree burns within a few minutes. Examples include small children reaching for boiling liquids on the table that fall down and scald their scalp and face, or burns from direct contact with fire or candles. Localized burns affecting the scalp have been reported after *cosmetic procedures* (Fig. 12.6a,b).

12.3.2.2 Treatment

Burns should be treated appropriately. At first, cool water should be applied, then dry sterile bandages. Children with more than 5% and adults with more than 10% of burnt body surfaces should be hospitalized. Prevention of superinfection, careful wound management, and treatment of pain are crucial. Usually the crust is not removed in the healing process [25]. Development of cancer in burn scars has been reported [14].

12.3.3 Freezing

Synonyms
frostbite alopecia

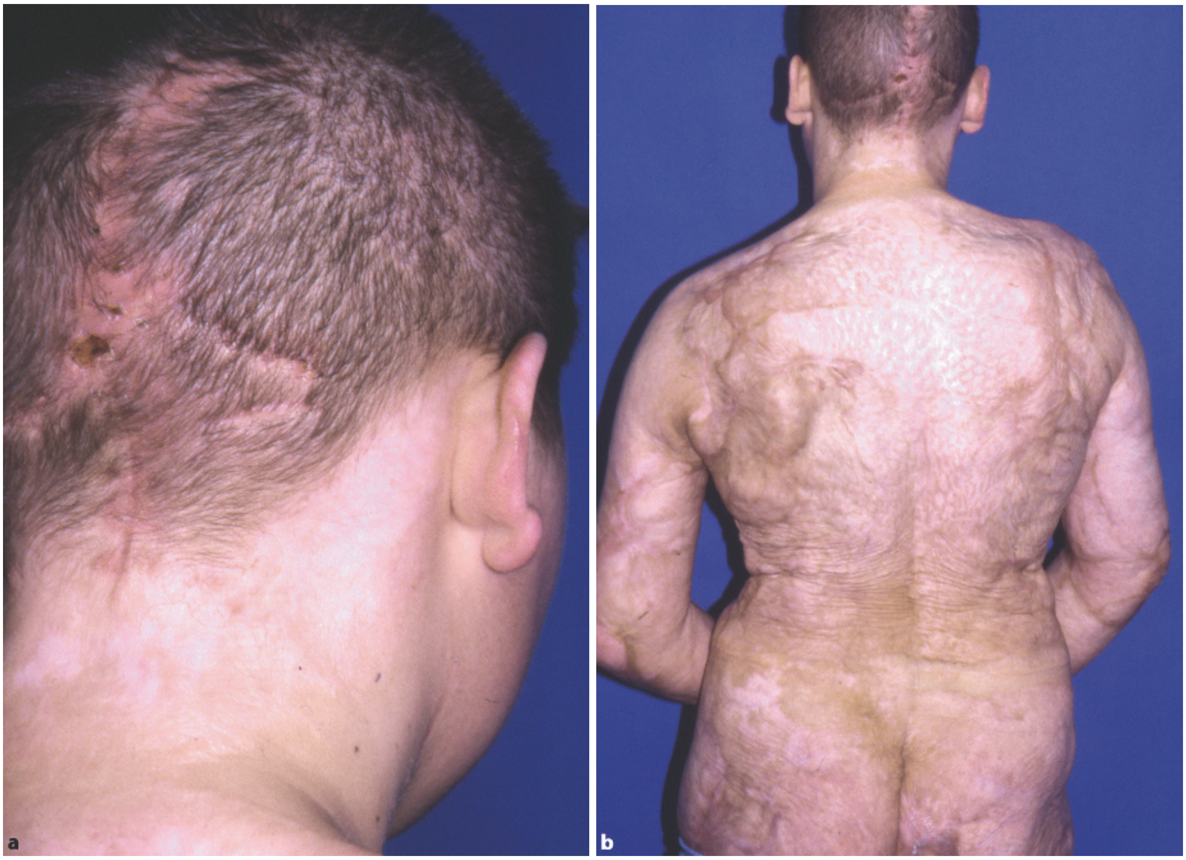


Fig. 12.6a,b Severe scarring after third-degree burn with scalp involvement. The scar on the scalp has been treated with a first session of scalp reduction surgery

Cicatricial alopecia can be caused by prolonged cold (laying on ice or snow) such as unconscious states in winter or mountain areas. Another cause is cryotherapy, for example when treating actinic keratosis of the scalp and when freezing time exceeds 10 seconds [24]. The patient should be warned of potential hair loss if hair-bearing areas are treated. Cryosurgery has been used for the treatment of eyelid trichiasis [125].

12.3.4 Chemical Injury

Synonyms
cauterization

12.3.4.1 Introduction

Acids, alkalis, and metallic salts may cause irreversible scalp damage, depending on their concentration and the duration of exposure. While acids cause a more superficial dry congealed necrosis, alkalis cause a deeper liquid necrosis. While some chemicals cause an immediate damage, others (such as organic substances) can cause a delayed or "protracted cauterization" [58]. There are reports of scarring alopecia due to improper application of hair styling substances, such as bleaching or perm preparations. Early neutralization of the chemical is crucial.

12.3.4.2 Clinical Features

Once scarred areas have developed, they are usually sharply demarcated and irregularly shaped.

12.3.4.3 Treatment

End-stage scarred lesions can be surgically treated. For smaller areas, scalp reduction (with or without use of a scalp expander) and/or hair transplantation can be performed [70, 77, 85, 137]. With hair transplantation, especially when micrografts (follicular units) are used, excellent results can be achieved without extensive surgery [8]. For larger areas, a scalp prosthesis may provide coverage.

12.3.5 Scratching

Synonyms
excoriation

Intense scratching in various itchy scalp conditions, such as dermatitis or infestations, can cause hair shaft damage and also scarring. Careful scalp examination including search for lice and nits is important. Management includes treatment of the underlying skin disorder, symptomatic anti-allergens and topical steroids or preparations containing menthol, urea or polidocanol. The nails should be cut short. Cotton gloves may be useful.

12.3.6 Insect Bites

Synonyms
tick bites

Alopecia from insect bites is rare and has been described after tick bites and from other insects such as ants. In tick bites, mainly from dog ticks and wild rabbit ticks, *Rickettsia conorii* is transmitted and can cause small necrotic papules and ulcers called tâches noires. These leave a small alopecic patch.

12.3.7 Radiation

Synonyms
chronic radiation dermatitis

Key Features

- Extent of damage correlates with dosage and other radiation characteristics.

Key Features

- A chronic radiation dermatitis with permanent alopecia can develop.
- Regular examination is mandatory because of increased risk of skin cancer.

12.3.7.1 Introduction

Radiation therapy with X-rays and ionizing rays has been used to treat intracranial and skull tumors as well as neoplasms of the scalp. Chronic radiodermatitis usually develops after 2 years and more from acute radio-

dermatitis, but a combination of radiation without radiodermatitis with chronic sun damage may gradually lead to similar changes. The extent of damage is determined by the quality of radiation (voltage and filters), dosage, fraction, distance from focus to skin, field size, and application time. Chronic radiodermatitis with permanent alopecia can develop if the X-ray dose exceeds 1200 cGy. There are differing data on the threshold above which permanent alopecia can develop. Scarring alopecia was reported to develop at doses above 300 cGy for deep, and 5000 cGy for soft, radiation. There is also a report about permanent alopecia above 700 cGy [136]. The degree of alopecia correlates with the dose per follicle [69].

12.3.7.2 History

In the first half of the past century, X-rays were frequently used for epilation in hypertrichosis or hirsutism and for ringworm treatment of the scalp. Though the latter procedure usually did not cause permanent alopecia, field overlap and mistakes in the procedure lead to permanent hair loss in some of these patients [4].

Radiation is still an important treatment modality for intracranial malignancies. Modern, more targeted techniques such as stereotactic radiation may decrease the incidence of chronic radiodermatitis.

12.3.7.3 Clinical Features

Poikilodermal features such as telangiectasia, pigment changes, and atrophy can be present. Often, the hair is not completely lost but appears finer and sparser. Depending on field size, the areas can be circumscribed or even mimic pattern hair loss. Radiation necrosis due to impaired blood supply can also develop, sometimes with a considerable delay. It presents as necrotic ulcers and can mimic carcinoma (Fig. 12.7a,b).

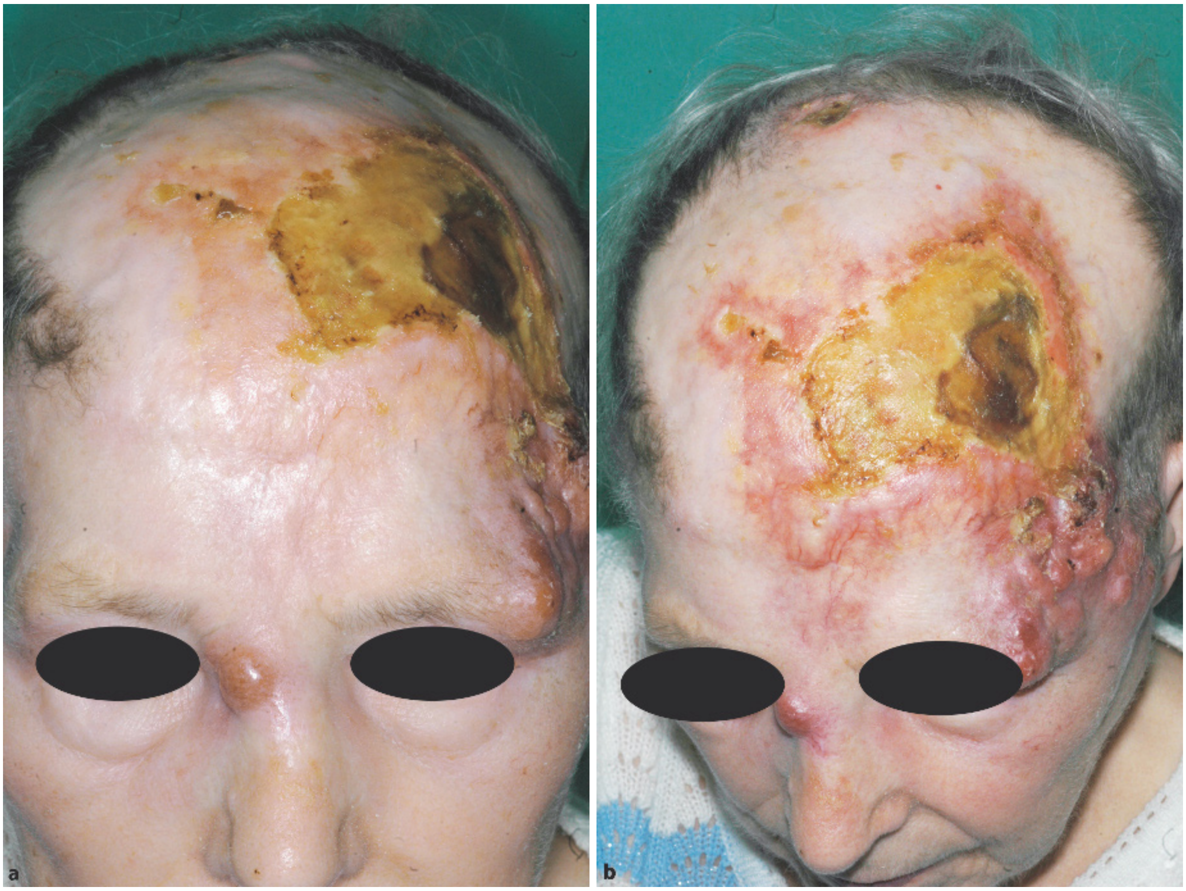


Fig. 12.7a,b Permanent alopecia after radiation of an angiosarcoma, which only led to temporary remission

12.3.7.4 Pathology

There is diffuse hyalinization of the dermal collagen, along with ectatic vessels. Atypical fibroblasts and radiation elastosis are present. Adnexal structures are lost.

12.3.7.5 Treatment

Once scarring from radiation or other traumas has occurred, plastic surgery is a therapeutic option. For small areas, surgery and flap skin transplantation can be performed [60]. Regular examination is mandatory because of the increased risk of epithelial tumor formation [81, 104]. Hair transplantation was performed in selected patients [89], but this makes follow-ups for cancer more difficult. Tempol, a nitroxide radioprotector (superoxide scavanger), is being evaluated in a topical formulation for prevention of whole-brain radiation- induced alopecia [80].

12

12.4 Infections

12.4.1 Bacterial

12.4.1.1 Carbuncle

A confluence of staphylococcal folliculitides may heal with scarring. A microbiologic culture usually reveals *Staphylococcus aureus*. Active lesions show a neutrophilic infiltrate, while extensive fibrosis of the fibrous tract and interstitial dermis develop later in the course. The diagnosis of folliculitis decalvans should be made if several lesions are present with a chronic course and a typical histology. Deeper cystic infiltration may represent dissecting cellulitis. Both conditions are discussed in Chap. 11. Topical and occasionally oral antibiotics are necessary, while a surgical intervention is only useful if an abscess has formed.

12.4.1.2 Leprosy

Synonyms
Hansen's disease, Lepra

Infection with *Mycobacterium leprae* can present in three clinical types depending on the resistance of the infected patient and the virulence of leprosy bacteria. There have been rare reports of scalp involvement and cicatricial alopecia in lepromatous leprosy [86], also following involvement of scalp from affected underlying skull. In lepromatous leprosy, colder skin areas are more likely to be affected [30], leading to facies leonina and loss of eyebrows and eyelashes (Lucio phenomenon).

12.4.1.3 Tertiary Syphilis

In the late stage of infection with *Treponema pallidum*, there is formation of gummas. They evolve in either the skin or underlying bone and often affect the scalp. Sharply demarcated necrotic ulcerations heal with polycyclic scars. Histologic features are tuberculoid granulomas with central necrosis and plasma cells. There is also endarteritis obliterans of dermal and subcutaneous vessels. For details on diagnosis and treatment, refer to the guidelines and recommendations of the WHO as well as the CDC (http://www.cdc.gov/STD/treatment/2-2002TG.htm#Syphilis) and the national societies of sexually transmitted diseases.

12.4.1.4 Cutaneous Tuberculosis

Synonyms
lupus vulgaris, tuberculous chancre, scrofuloderma, miliary tuberculosis

A chronic infection with *Mycobacterium tuberculosis* or *bovis* mainly occurs through endogenous reinfection from lymph nodes or bone or hematogenous spread from other organs, affecting the head and neck (acral areas) in 80% of cases and frequently involving the scalp [64, 146]. The red and beige granulomatous tumors initially cause displacement alopecia and heal with a scar.

12.4.2 Viral

12.4.2.1 Zoster and Varicella

Synonyms
shingles, chicken pox

Varicella typically affects the scalp and usually does not heal with scars. They can however develop from scratching of the itchy lesions, superinfection or when keloids result [75]. The necrotizing form of segmental zoster (segments V1, C2/3) may also cause scarring alopecia, as well as artifactual excoriation due to dysesthesia (Fig. 12.8a,b).

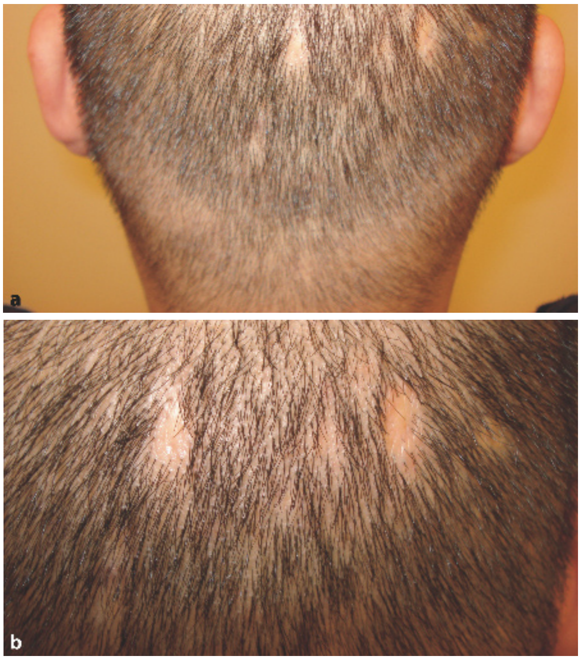


Fig. 12.8a,b Small scars developed after excoriation of itchy varicella lesions

12.4.3 Fungal

12.4.3.1 Tinea Capitis

It may be debated whether tinea capitis should be considered a primary scarring alopecia, as the follicle is the target of fungal infection. Chronic or highly inflammatory tinea capitis can lead to scarring.

12.4.3.1.1 Kerion

Synonyms
kerion celsi, tinea capitis profunda

Key Features

- A highly inflammatory, suppurative tinea capitis, usually caused by zoophilic fungi.
- Bacterial superinfection may occur.
- Systemic and topical antifungals should be used and may have to be combined with antibiotics and oral prednisone initially.

12.4.3.1.1.1 Introduction

Kerion is a deep, highly inflammatory fungal infection of the scalp. It can cause scarring alopecia and should therefore be aggressively treated.

12.4.3.1.1.2 History

The term kerion was coined by Aulus Cornelius Celsus 30 bc to 50 ad, as the lesions sometimes resemble a honey comb (kerion in latin).

12.4.3.1.1.3 Epidemiology

Animals can be the source of infection. Children are affected far more commonly than adults.

12.4.3.1.1.4 Pathogenesis

Typical causes of kerion are zoophilic fungi, especially *Trichophyton verrucosum* and *Trichophyton mentagrophytes var. granulosum* (both ectothrix), but also geophilic fungi.

Various *Trichophyton* and *Microsporon* species have been reported in kerion, such as *Trichophyton mentagrophytes*, *Microsporum gypseum*, *Trichophyton rubrum*, and *Trichophyton sulphureum*.

The severity of the infection is determined by the pathogenicity of the organism as well as the host immune response, the latter being much exaggerated in kerion. In cases of *Trichophyton rubrum* on the scalp, underlying disorders such as diabetes, malignancies, and other immune defects should be ruled out.

There have also been reports of induction of kerion by topical steroid application to less inflammatory tinea capitis.

12.4.3.1.1.5 Clinical Features

A highly suppurative, boggy, nodular deep folliculitis with fistulas and pus secretion from several openings is present. Regional lymphadenopathy is frequent, sometimes with headache and fever.

Potassium hydroxide (KOH) examination can be performed but cultures (of scales and epilated hairs) are necessary to confirm the diagnosis and specify the fungus, also for epidemiological reasons (Fig. 12.9a,b).

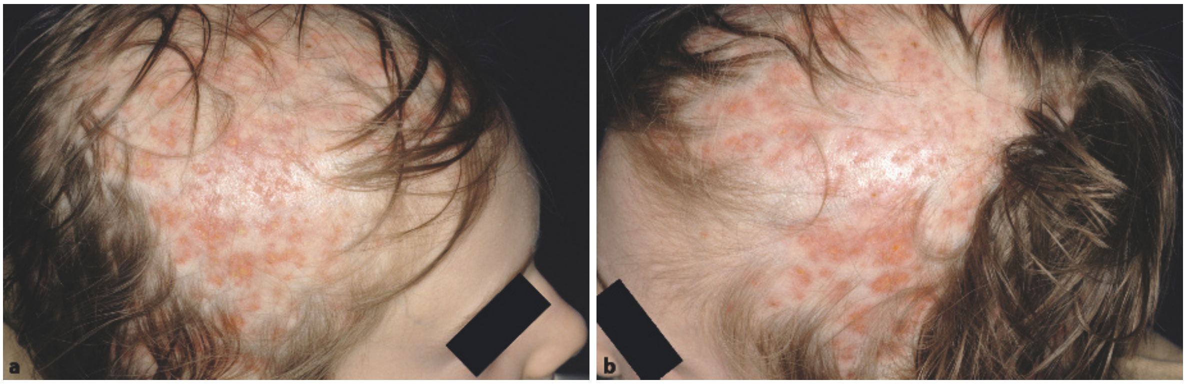


Fig. 12.9a,b Kerion

12.4.3.1.1.6 Pathology

If a biopsy were taken, the histology may be similar to a dissecting cellulitis. There are widened and ruptured follicles. The infiltrate is initially neutrophilic, but becomes mixed and granulomatous in the course of the condition. Fungal stains (PAS) can confirm the diagnosis.

12.4.3.1.1.7 Differential Diagnosis

Kerion celsi can mimic dissecting folliculitis [93, 121] or erosive pustular dermatosis [78].

12.4.3.1.1.8 Treatment

Proper management is important to prevent alopecia and unnecessary hospitalization [102]. Systemic antifungals are indispensable for treating this condition [36, 50] (see Table 12.2). In severe cases, treatment may be started before confirmation by culture, when the native KOH examination is positive. Cultures should be performed at biweekly follow-up visits. Treatment should be continued until KOH examination and cultures are negative.

Griseofulvin has been the gold standard for therapy since it was introduced in 1959 and is approved for this indication and also for children. It is still recommended by most authors as first-line therapy. This benzofuran fungistatic has to be taken with a fatty meal. The recommended dosage for ultramicrosize griseofulvin is 10 mg/kg per day (maximum 500 mg/d); for microsize griseofulvin, 20 mg/kg per day.

Newer antifungals such as the allylamine terbinafine and the azoles itraconazole and fluconazole have been advocated [41, 82, 91, 109]. Although only approved for children in some countries and under certain conditions, they have a better safety profile, fewer drug interactions, and may require shorter treatment periods. For young children and longer treatment periods, liquid preparations, especially fluconazole, are increasingly used.

The role of adjunctive systemic corticosteroids in kerion celsi is controversial [56], but in certain severe cases low-dose prednisone in the first weeks appears to improve the outcome, inhibiting the excessive destructive inflammatory reaction to the fungus [63]. Intralesional steroids could not improve the outcome in a controlled trial [48].

Systemic antifungal treatment should always be combined with a synergistic topical treatment of scalp and hair, for example containing sporicidal ciclopirox olamine [112]. This, along with trimming the hair, can shorten treatment duration and reduce contagiousness by reducing the fungal load. Additionally, sporicidal shampoos containing ketoconazole or selenium disulfide are also recommended. These recommendations may especially apply to children who produce less sweat and sebum, which usually transport antifungals to the distal hair shaft.

Depending on microbiology results, antibiotics may have to be added as bacterial superinfection often occurs.

Adequately treated children may still attend school, at the latest 2 weeks after treatment initiation. Contact persons should be examined, also to identify asymptomatic carriers. Those should be treated with an antifungal shampoo twice weekly. The same applies to pets. Combs, hats, and other utensils have to be disinfected or discarded.

Surgical intervention should only be considered in exceptional cases but can be helpful to restore scarred areas [37, 66, 128] (Table 12.2).

Table 12.2 Treatment regimen for systemic antifungals, duration may have to be extended until mycological and clinical cure

Agent	Dose	Duration (weeks)
Griseofulvin (microsize)	20 mg/kg per day (max. 1000 mg/day)	6–8
Itraconazole	5 mg/kg per day	4–8
Fluconazole	6 mg/kg per day (over 6 months old)	3–6
Terbinafine	62,5 mg/day per day (10–20 kg) 125 mg/day (20–40 kg) 250 mg/day (>40 kg)	2–4

12.4.3.1.2 Favus

Synonyms
favus cicatricans, tinea favosa

Key Features

- A chronic infection by *Trichophyton schoenleinii*, usually transmitted after prolonged contact.
- Yellow scutula crusts are specific with underlying erosions and ulcerations.

12.4.3.1.2.1 Introduction

Favus is a chronic superficial dermatophyte infection characterized by sulfuric-yellow crusts, in severe cases leading to central atrophy with centrifugal spreading.

12.4.3.1.2.2 History

The causative fungus, *Trichophyton schoenleinii*, was discovered by Schoenlein in 1839. Spontaneous remission is rare, very often year-long close contact is necessary for transmission. For this reason, usually only family members used to infect each other [11, 61] and the condition was long thought to be hereditary.

12.4.3.1.2.3 Epidemiology

Infections have been reported from families in Eastern Europe, the Mediterranean countries, the Balcans and the Near and Middle East. Endemic areas also exist in Northern Africa and parts of Brazil and Mexico. In Western Europe and North America the condition is rare and few endemic areas have been reported. Families with many children are more commonly affected.

12.4.3.1.2.4 Pathogenesis

Although the anthropophilic dermatophyte *Trichophyton schoenleinii* is the usual cause, favus-like cases have been reported from other fungi. Constantly covered scalp may be more susceptible.

12.4.3.1.2.5 Clinical Features

Typical are small, yellow, scaly cuplike crusts of up to 2 cm in diameter, called scutula. They are often pierced by one or several hair shafts. Their smell was described as being reminiscent of mouse urine. These scutula consist of keratin debris and hyphae. There is usually no hair breakage, as the hair shaft is not completely affected. The scutula develop on an erythematous, sometimes ulcerative base, which may result in scarring after years. In Wood's light, bluish-white fluorescence can be observed. Glabrous skin may also be affected.

12.4.3.1.2.6 Pathology

There is formation of air spaces between hyphae within the infected hair. These air tunnels form as a result of autolysis of the hyphae. Arthroconidia rarely are seen within the hair.

12.4.3.1.2.7 Differential Diagnosis

Other scaling scalp conditions can resemble favus.

12.4.3.1.2.8 Treatment

All affected family members should be treated simultaneously. Griseofulvin is the standard treatment. Longer treatment periods than for other forms of tinea capitis may be required. In vitro studies indicate that *T. schoenleinii* is sensitive to newer antifungal drugs, similar to other dermatophytes. Therefore, griseofulvin is increasingly replaced by newer antifungals [34].

12.5 Inflammatory Dermatoses

12.5.1 Psoriasis

Key Features

- Sharply circumscribed erythemato-squamous plaques extending over the hairline.
- A rare cause of scarring alopecia.
- Keratolytics and anti-inflammatory topicals usually control the condition.

Although the scalp is frequently affected in psoriasis, there have been very few reports of a permanent psoriatic alopecia [7, 19, 65, 106, 107, 114, 138, 145]. Psoriasis is a very common inflammatory dermatosis with dermal inflammation and hyperparakeratosis. It can be more severe in patients positive for human immunodeficiency virus (HIV) and there has been a report of scarring alopecia in such a case [111]. The sharply circumscribed erythemato-squamous plaques usually extend beyond the hairline. Itching is common in scalp psoriasis [126]. If only the scalp is affected, differentiation from seborrheic dermatitis can be difficult, and many authors think these conditions are closely related. Various topical treatment options in different formulations are available for scalp psoriasis [139].

12.5.2 Pityriasis Amiantacea

Key Features

- Very scaly, non-specific scalp condition.
- Removal of scales can cause permanent alopecia.

This massively scaly scalp condition can result in permanent alopecia [68, 83], most likely in combination with mechanical manipulation when the scales are removed. Most likely, this condition represents a morphologic reaction pattern of the scalp in chronic irritation, such as seborrheic dermatitis and contact dermatitis. It may also represent severe psoriasis in some cases. A recent case series in Egypt found psoriasis in 35.3% and dermatitis in 34.2% of patients, while 12.9% had tinea capitis [1]. Insufficient hygiene and infrequent shampooing may contribute. Multiple hairs are uprooted by attempts to remove the scales. This repeated plucking in combination with inflammation can result in permanent alopecia.

Clinically, mica-like adherent white scales extend onto the hair shafts. They have been compared with asbestos. Retroauricular rhagades are often associated. Pruritus is an uncommon feature. On histology, there is a massive hyperkeratosis. Spongiotic folliculitis and perifolliculitis can sometimes be seen. Underlying conditions should be diagnosed and treated specifically, especially tinea capitis.

12.5.3 Giant Cell Arteritis

Synonyms
temporal arteritis, Horton's disease, cranial arteritis

Key Features

- Granulomatous panarteritis..

Key Features

- Presents as tender, pulseless, indurated temporal artery, which can lead to ulceration and subsequent scarring.
- Systemic manifestations include blindness, headache, and jaw claudication.
- Polymyalgia rheumatica can be associated in 50%–75%.

This is a systemic granulomatous vasculitis. The temporal artery is most often affected, at times together with other extracranial vessels. Rarely, other large vessels such as the aorta are involved. Scalp necrosis is a rare complication. This can lead to cicatricial alopecia [13,

22, 29, 96, 105, 118]. A prolonged course of systemic steroids for at least 6 months up to 2 years is usually necessary, also to prevent blindness [88]. Methotrexate (MTX) can be added as a steroid-sparing agent. Topical wound care should be applied to prevent superinfection and facilitate healing. Recurrences are not uncommon. A self-limited course after several years has been observed (Fig. 12.10a,b).

12.5.4 Pyoderma Gangrenosum

Synonyms
pyoderma gangraenosum

This condition very rarely occurs on the scalp, presenting as a necrotic, painful, non-infective, rapidly enlarging ulcer, typically with an undermined border [95, 101, 117, 140]. Osteolysis is a very rare association. In about 50% of cases, there is an underlying systemic disorder, such as inflammatory bowel disease, a myeloproliferative malignancy, rheumatoid arthritis or chronic hepatitis. Management involves careful wound care, treatment of the underlying condition and the use of immunosuppressing agents.

12.5.5 Graft-Versus-Host Disease (GVHD)

Key Features

- A common sequela after bone marrow or stem cell transplantation.
- Acute GVHD (50%) includes enteritis, dermatitis, and hepatitis.
- In chronic GVHD (10%), skin lesions are lichenoid and sclerodermiform.
- Hair follicles can also be destroyed by the infiltrate.
- Immunosuppressants are used, especially to treat other involved organs.

With the rising numbers of allogenic bone marrow or autologous stem cell transplantation, this disorder is of increasing importance. It occurs when foreign immunocompetent cells are transplanted into an immunoincompetent host. Acute GVHD can become chronic when lasting for more than 100 days or chronic GVHD may develop de-novo in 20%–30% of cases. In these cases, various other organs can be affected and the prognosis is less favorable. Cytotoxic folliculitis was reported in acute GVHD [87]. Clinically, lichenoid papules are followed by scleroderma-like lesions, resulting in cicatri-



► **Fig. 12.10a,b** Arteritis temporalis with scalp necrosis. A typical histology with a narrow lumen, and a variable infiltrate of the vessel wall with bizarre giant cells confirms the diagnosis

cial alopecia [17]. Systemic immunosuppressants such as ciclosporin, steroids, azathioprine, and cyclophosphamide are the treatment of choice. Psoralen plus UV A light therapy (PUVA) and UVA1 are effective against lichenoid lesions. Halofuginone, a topically applied inhibitor of collagen type I synthesis, was reportedly beneficial in patients with sclerodermatous GVHD [97]. Thalidomide has also been used. Other treatments include anti tumor necrosis factor alpha (TNFα) antibodies, immunoglobulins and extracorporeal photopheresis as well as topical tacrolimus (Fig. 12.11a–c).

12.5.6 Morphea and Facial Hemiatrophy

Synonyms
circumscript scleroderma, linear morphea, scleroderma en coup de sabre

Key Features

- Circumscribed hyalinization of collagen and destruction of follicles, atrophy with loss of subcutaneous fat.
- Most likely due to autoimmune mechanisms.

Key Features

- Linear morphea is the most common form, affecting the scalp and forehead.
- Underlying structures, such as the skull, may be affected.

12.5.6.1 Introduction

Morphea is a localized form of scleroderma and can cause cicatricial alopecia. A linear form of morphea affecting the frontal scalp has been termed *linear scleroderma en coup de sabre* (LSCS) (Fig. 12.12). Ocular and neurologic abnormalities can be associated.

12.5.6.2 Epidemiology

While LSCS represents the most common cause of cicatricial alopecia in early childhood, *circumscribed scleroderma* (morphea) rarely affects the scalp and is up to three times more frequent in women. In a collection of 750 children with juvenile scleroderma, 65% had linear scleroderma [147].

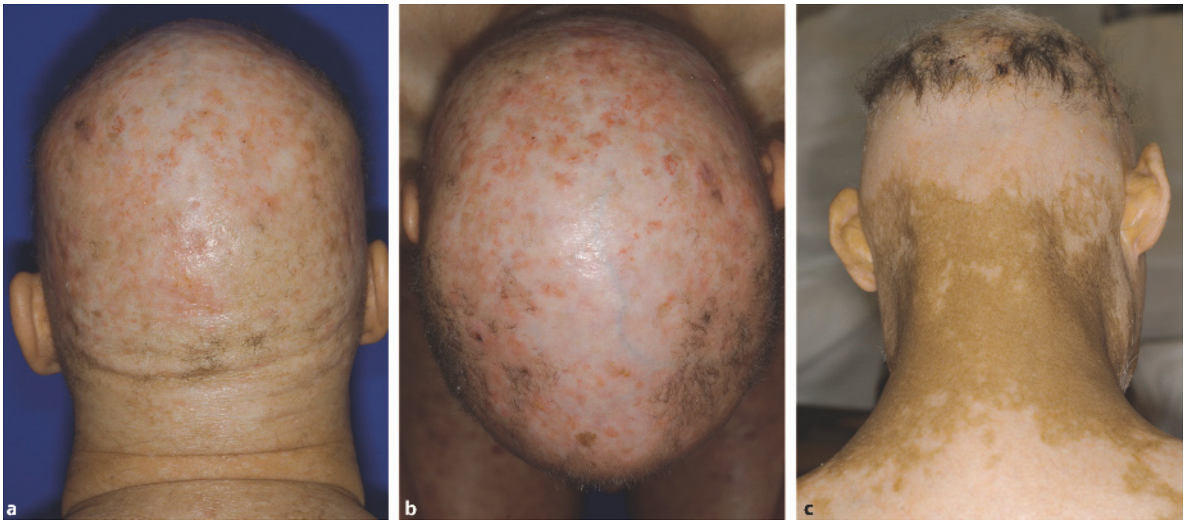


Fig. 12.11a–c Chronic graft-versus-host disease (*GVHD*) with poikiloderma and alopecia



Fig. 12.12 Scarring alopecia in morphea



Fig. 12.13a–c Scleroderma en coup de sabre with eyebrow involvement

12.5.6.3 Pathogenesis

Autoimmunity is thought to be involved. ANA (antibody to nuclear antigens) is positive in a number of cases. Possible etiologic factors for the alopecia include inflammatory infiltrate or cytokines and later displacement and pressure. In the linear forms, genetic mosaicism leading to a distribution in the lines of Blaschko is discussed [119]. The role of *Borrelia* infection is unclear.

12.5.6.4 Clinical Features

In early morphea, a lilac macule extends centrifugally and develops into a centrally atrophic plaque with a white shiny surface and a depression. The lilac edge signals activity, but may be absent in scalp lesions. The hair is shed early in the process, followed by sclerotic alopecia.

In LSCS, a yellow-ivory discoloration develops into a linear depression with minimal inflammation and a shiny surface. It extends from the scalp over the forehead resembling a saber cut, due to atrophy of the galea aponeurotica and underlying skull. While eyebrow involvement is not uncommon, loss of eyelashes is very rare [39]. A neurologic and ophthalmologic examination is recommended. Magnetic resonance imaging (MRI) has been shown to be superior to electroencephalography (EEG) in detecting early CNS involvement (Fig. 12.13a–c).

12.5.6.5 Pathology

Early histologic signs include a superficial and deep perivascular infiltrate with lymphocytes and plasma cells. Later, hyalinized and thickened collagen bundles develop. There is loss of follicles and sebaceous glands, and the sweat glands are enclosed in the sclerotic corium. Elastic stain shows a normal pattern. Because these features do not represent true fibrosis with damage to elastic tissue, permanent hair loss in morphea has been categorized as a pseudo-cicatricial alopecia.

12.5.6.6 Differential Diagnosis

Scalp morphea may resemble alopecia mucinosa or other localized scarring alopecias. LSCS may be a minimal form of the rare *facial hemiatrophy (Parry-Romberg syndrome)* and overlaps have been observed [120]. In this condition, subcutaneous fat, muscle, and bone can be affected and the skin is only secondarily affected without prominent sclerosis. Ocular as well as CNS manifestations are common. A dysfunction of the sympathetic nerves has been postulated (trophoneurosis). This hypothesis is supported by reports of development of the condition after sympathectomy and the distribution along the branches of the trigeminal nerve, which is accompanied by sympathetic fibers.

12.5.6.7 Treatment

The role of *Borrelia* infection and the use of antibiotics are controversial. Systemic treatment with penicillin, ceftriaxon or doxycycline is especially recommended in the European literature.

Ciclosporin, iloprost and oral steroid pulse therapy in combination with methotrexate have been used in active and extensive cases of morphea [135].

Intralesional (triamcinolonacetonid 10 mg/ml) and topical steroids are used for localized lesions. Occlusive tacrolimus has also been successfully used [72]. The role of antimalarials and vitamin-D_3 derivatives has to be evaluated [31]. The latter have been used in combination with PUVA for LSCS [45]. Our experience with topical calcipotriol has been positive in terms of decreasing inflammation and preventing spread (personal observation). Flap and expander techniques as well as fat or polyethylene implantation are surgical treatment options [23, 35, 92, 110].

12.5.7 Lichen Sclerosus and Atrophicus

Synonyms
lichen sclerosus and atrophicans (LSA)

This condition most commonly affects the genital mucosa, sometimes the trunk. There have been single reports of scalp involvement with alopecia. Initially, porcelain-white papules expand and then develop into atrophic plaques. The scalp can be affected in patients with multiple lesions [12]. In one report, pruritic lesions caused extensive scarring alopecia [42]. In another case, there was bullous LSA with scalp involvement [73]. Topical and intralesional steroids are used in this condition [44], acitretin has also been successfully used in one patient with scalp involvement [9].

12.5.8 Cicatricial Pemphigoid

Synonyms
benign mucous membrane pemphigoid, scarring pemphigoid, ocular pemphigus, desquamative gingivitis, CP type Brunsting-Perry

Key Features

- A chronic autoimmune subepidermal bullous disorder mainly affecting the mucous membranes.
- A phenotype shared by different diseases with predilection for the mucosal surfaces.
- Skin and especially scalp involvement is rare but can cause cicatricial alopecia.

This chronic autoimmune bullous disorder predominantly affects the conjunctiva, oral, nasal or genital mucous membranes. The skin is involved in around 24% of cases [2], typically with a few lesions on the face and scalp. In a series of 54 patients, only 4 had scalp involvement [6]. In the Brunsting-Perry variant, only the skin is affected and the prevalence is higher in men. There is no tendency for spontaneous remission. When the scalp is affected, recurrent, tense or flaccid bullae and erosions are usually present in a limited area and lead to cicatricial alopecia [47, 67].

12.5.9 Porphyria Cutanea Tarda

Synonyms
scleroporphyria, porphyrinic alopecia, PCT

Key Features

- A photosensitive dermatosis due to porphyrin accumulation.
- Pseudoscleroderma can rarely develop and cause scarring alopecia.

12.5.9.1 Introduction

Photosensitizing porphyrins can lead to UV-induced formation of blisters and milia, hyperpigmentation, and subsequent scarring. There have been several reports of resulting alopecia [57, 59, 99].

12.5.9.2 Epidemiology

Porphyria cutanea tarda is the most common type of porphyria, affecting about 1% of the population, mostly men between the ages of 40 and 70.

12.5.9.3 Pathogenesis

Porphyria cutanea tarda is an acquired (80%) or inherited (20%, autosomal-dominant defect on 1p34) disorder with defective uroporphyrinogen-decarboxylase leading to activation of ALA-synthetase and accumulation of photosensitizing uroporphyrin. Both forms can be differentiated by measurement of the enzyme activity. Often, there is an additional factor such as underlying liver dysfunction. Patients should be checked for alcohol intake, elevated transaminases, hepatitis, hemochromatosis, ferritin elevation, estrogen intake, and liver-toxic drugs.

12.5.9.4 Clinical Features

Typical features of porphyria cutanea tarda on sun-exposed sites are milia, blisters, hyperpigmentation and hypertrichosis. It has been described as usually extending from the neck upwards to the vertex area leaving a sclerodermiform induration of the scalp with porphyrinic alopecia [100]. Porphyrins in the urine are elevated giving it a Bordeaux color.

12.5.9.5 Pathology

There is thickening and homogenization of the follicular connective tissue sheath followed by shedding. Subepidermal blistering can occur.

12.5.9.6 Treatment

Aggravating factors (alcohol, sun exposure) should be avoided. The standard treatment is chloroquine 250 mg weekly. With treatment initiation, fever and joint pain can occur. Phlebotomy of 500 ml every 2 weeks is traditionally used. Desferoxamine and erythropoietin are only used if the standard treatments are contraindicated.

12.5.10 Epidermolysis Bullosa Acquisita

Acquired epidermolysis bullosa can also cause scarring alopecia due to antibody formation directed against the NC1 domain of collagen VII. Blisters with subsequent scar and milia formation develop in mechanically stressed areas. Direct and indirect immunofluorescence are used to exclude the differential diagnosis of bullous pemphigoid. Immunosuppressants are used to control the condition.

12.5.11 Sarcoidosis

Synonyms
Morbus Boeck, Besnier-Boeck-Schaumann disease, Boeck's sarcoid

Key Features

- A systemic granulomatous condition of unknown origin.
- Scalp involvement is rare but can cause cicatricial alopecia.

12.5.11.1 Introduction

Sarcoidosis is a systemic disease characterized by non-caseating epithelioid-cell granulomas affecting the skin (25%) and other organs such as the lung and hilar lymph nodes. Cicatricial alopecia has been reported to result from scalp involvement but also in the beard area.

12.5.11.2 History

Jonathan Hutchinson described the first case of sarcoidosis in 1869.

12.5.11.3 Epidemiology

A bimodal age distribution is seen. Most patients are usually younger than 40, another peak is at 45–65 years. The incidence is 20–30/100,000. In Europe Scandinavians have the highest risk. The condition occurs worldwide. However, the incidence is up to 10 times higher in patients of color, especially women. In a review of the English-language literature, 24 cases with scalp involvement were found, most of them in African-American women [62].

12.5.11.4 Pathogenesis

Unknown. A chronic granulomatous immune reaction has been thought to be provoked by an unknown antigen. On the other hand, B-cell activity is increased while T-cell function is impaired. The latter can be demonstrated with a negative intracutaneous test towards recall antigens, such as tuberculin. A defect on chromosome 6, causing a diminished synthesis of the protein BTNL2, has shown to increase the risk of sarcoidosis. This protein is involved in leukocyte activation.

12.5.11.5 Clinical Features

Small orange-brown or livid-red confluent papules are typical, often extending from the hairline. Diascopy shows an apple jelly color. Lymphadenopathy may be present. A thorough work-up is required as systemic involvement is present in nearly all patients, often heralded by the skin lesions. Besides the skin, pulmonary lymph nodes, lungs and joints are most commonly involved. An elevation in angiotensin converting enzyme (60%) and calcium (49%) are laboratory markers.

12.5.11.6 Pathology

Scattered superficial and deep "naked" sarcoidal granulomas can be found.

They are well circumscribed and contain giant cells as well as Langerhans cells. Giant cells may contain asteroid or Schaumann bodies. There is also a chronic lymphocytic perifollicular infiltrate. Fibrosis, if present, usually starts at the periphery of the lesion.

12.5.11.7 Differential Diagnosis

Tuberculosis (lupus vulgaris) can be differentiated by necrosis in the center of the granulomas and a positive Ziehl-Neelsen stain. Other differential diagnoses include necrobiosis lipoidica, cutaneous lymphomas, cutaneous lupus erythematosus, and mucinosis follicularis.

12.5.11.8 Treatment

Topical (occlusive) and intralesional steroids are most successful [49]. Other options include tacrolimus, tazarotene and photodynamic therapy. Oral steroids and methotrexate are used in systemic disease. The evidence on the efficacy of antimalarials and retinoids is sparse (Fig. 12.14).



Fig. 12.14 Nodular sarcoidosis with secondary scarring alopecia

12.6 Drugs

12.6.1 Drug-induced Permanent Hair Loss

Synonyms
drug-induced permanent alopecia

Key Features

- Most drugs cause temporary alopecia.
- Permanent complete or partial hair loss is exceptional.

12.6.1.1 Introduction

Drugs can occasionally cause permanent alopecia by irreversibly destroying hair follicles. This has been reported from some cytostatic drugs such as in polychemotherapy, retinoids, gold [16], and busulfan [129, 130]. Severe drug reactions (erythema multiforme, toxic epidermal necrolysis) can also result in consecutive pseudo-cicatricial alopecia.

12.6.1.2 Pathogenesis

Unknown, but it is believed that these drugs may lead to depletion of stem cells or the destruction of dermal papilla cells.

12.6.1.3 Clinical Features

Often there is not complete alopecia, but a permanently decreased hair density presenting as sparse, finer hair.

12.6.1.4 Treatment

Minoxidil topical solution before and after the use of cytostatic drugs has been shown to delay hair loss and accelerate regrowth in *non-permanent* alopecia [32]. Application of ice-packs has been claimed to reduce the toxic effects of anti-metabolites on the scalp but bears the potential risk of diminished efficacy to treat the malignancy.

12.7 Neoplasms

These conditions are discussed in Chap. 18.

Summary for the Clinician

Permanent or secondary scarring alopecia can result from various non-follicular scalp conditions leading to destruction of the pilosebaceous unit. Trauma, deep infections or tumors can be localized on the scalp and often lead to alopecia. Other alopecic lesions may result from an inflammatory or genetic skin condition with a variable frequency of scalp involvement and alopecia. While some are true dermatoses, skin and scalp lesions are a marker for systemic disease in others.
If loss of follicular ostia, atrophy, sclerosis or signs of inflammation are present, a deep biopsy, preferably at the active edge of the lesion, may help to find the underlying specific cause. A thorough examination and a careful history as well as other tests may aid in the diagnosis.
In active disease, sufficient and timely treatment may prevent progression of the alopecia and possible systemic involvement. Surgical management, especially hair transplantation, is an option in end-stage lesions.

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Chapter 13

Diffuse Hair Loss

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13

Synonyms

Diffuse hair loss, anagen effluvium, dystrophic anagen effluvium, chemotherapy-induced alopecia, radiation-induced alopecia, toxic alopecia, loose anagen hair, AIDS trichopathy, telogen effluvium, immediate anagen release, delayed anagen release, immediate telogen release, delayed telogen release, short anagen, acute telogen effluvium, postfebrile effluvium, postpartum effluvium, psychogenic effluvium, seasonal telogen effluvium, chronic telogen effluvium, iron deficiency, female pattern hair loss, psychogenic pseudoeffluvium, diffuse alopecia areata, diffuse alopecia with stem cell folliculitis

Key Features

- Many factors can lead to pathologically increased hair loss. The pathologic dynamics of hair loss can be related to disorders of hair cycling.
- Telogen effluvium is hair loss that results from increased shedding of hairs from the telogen phase of the hair cycle. On the basis of changes in different phases of the follicular cycle, telogen effluvium is classified into varied functional types.
- Telogen effluvium presents either as an acute and diffuse hair loss brought about by a variety of triggers, or as chronic telogen effluvium, which is defined as diffuse telogen hair loss that persists >6 months with unexplored or unknown etiologies.
- Management of diffuse hair loss depends on the cause and underlying pathomechanism in its relation to the hair growth cycle. Once the diagnosis is established, treatment appropriate for that diagnosis is likely to control the hair loss. Chronic telogen effluvium of unknown origin can be satisfactorily handled with unpatronizing sympathy and by firm exposition of the dynamics of hair growth.

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13.1 Introduction

Few dermatologic complaints carry as much anxiety and emotional distress as hair loss. Equally, evaluation and management of hair loss are challenging. Most vexing may be the adult female presenting with diffuse hair loss [16]. Some men take the state of their hair seriously [14]; practically all women do [15]. The emotional overtones in this situation are often great; in some cases they seem disproportionate to the extent of hair loss. Misconceptions arise, as the patient obtains erroneous information from friends, hair dressers, and pharmacists [78]. Adding to the patient's worry may be prior negative experiences with physicians, who trivialize complaints of hair loss. This attitude on the part of physicians may result from lack of knowledge, thereby making them uncomfortable dealing with such patients. Knowledge of the main types of hair loss is a prerequisite to providing appropriate patient care. Moreover, in addition to its obvious psychological importance, hair loss may be a manifestation of a more general medical problem.

13.2 History

Diffuse shedding of hair has been called "defluvium capillorum." Sabouraud in 1932 [60] originally restricted the term to sudden diffuse loss of hair following shortly after a severe emotional shock, while others applied it to all forms of alopecia. During the 1950s "chronic diffuse alopecia" in women was differentiated from acute and reversible diffuse alopecia, attributable to a readily identifiable cause [72]. However, a majority of these patients were women with androgenetic alopecia of the female pattern who did not display any endocrinological abnormalities. The term was also used to describe women with diffuse hair loss of unexplored etiology, such as thyroid dysfunction or malnutrition. In 1960 Guy and Edmundson [28] described a form of chronic diffuse hair loss they called "diffuse cyclic hair loss in women" in which no specific trigger was evident. Finally, others assumed that a diffuse type of alopecia areata may account for some cases of alopecia diffusa [10]. In 1961 Kligman revealed the pathodynamics of one common pattern of response of hair follicles to a variety of insults and named it telogen effluvium [37]. On the basis of changes in different phases of the follicular cycle, Headington [32] later (in 1993) proposed classification of telogen effluvium into five functional types based on changes in different phases of the hair cycle, while Whiting [81] finally revived the concept of chronic telogen effluvium, additionally characterizing histopathologic features that delineate this entity from androgenetic alopecia.

13.3 Pathogenesis

Disease states that cause hair loss are categorized according to whether the hair loss is diffuse or localized, and to whether the follicle remains intact or is destroyed and replaced by scar. Except for the scarring alopecias, hair loss represents a disorder of hair follicle cycling [53]. Whatever the cause, the follicle tends to behave in a similar way. To grasp the meaning of this generalization requires understanding of the hair cycle and its derangements.

13.3.1 Hair Follicle Cycling

The hair follicle is subject to constant turnover in the course of perpetual cycles through phases of proliferation (anagen), involution (catagen), and resting (telogen), with regeneration in the successive hair cycle [54].

It is a major characteristic of *anagen* that not only is the hair shaft growing but most epithelial hair follicle compartments are undergoing proliferation, with the hair matrix keratinocytes showing the highest proliferative activity.

During *catagen*, hair follicles enter a process of involution that is characterized by a burst of programmed cell death (apoptosis) in the majority of follicular keratinocytes [6]. The resulting shortening of the regressing

epithelial strand is associated with an upwards movement of the follicle.

In *telogen*, the hair shaft matures into a club hair, which is held tightly in the bulbous base of the follicular epithelium, before it is eventually shed. It is still unresolved whether shedding of the telogen hair (teloptosis) is an active, regulated process or represents a passive event that occurs at the onset of subsequent anagen, as the new hair grows in [57].

Cyclic hair growth activity occurs in a random mosaic pattern with each follicle possessing its own individual control mechanism over the evolution and triggering of the successive phases, though systemic factors such as the hormonal system, cytokines and growth factors, as well as external factors linked to the environment, such as toxins, and deficiencies of nutrients, vitamins, and energy.

Finally, there are considerable variations in the length of these phases depending on the body site location, with the duration of anagen determining the type of hair produced, particularly its length [54]. On the scalp, hairs remain in anagen for a 2- to 6-year period of time, whereas telogen lasts for approximately 100 days, resulting in a ratio of anagen to telogen hairs of 9:1. On average, the amount of new scalp hair formation matches the amount that is shed, thereby maintaining a consistent covering. With a range of 75,000 to 150,000 hairs on the head, the reported average daily number of telogen hairs being shed varies, with published values of 35 [35], 40–100 [61], 100 [61, 71], 100–150 [21], and 100–180 hairs [80]. In general, the anagen phase is longer in women than in men [21].

13.3.2 Pathologic Dynamics of Hair Loss

Many factors can lead to pathologically increased hair loss. The pathologic dynamics of hair loss can be related to disorders of hair cycling.

13.3.2.1 Dystrophic Anagen Effluvium

Dystrophic anagen effluvium is hair loss that results from the shedding of large numbers of hairs from the anagen phase of growth. It is a major characteristic of anagen that the epithelial hair follicle compartment undergoes proliferation, with the hair matrix keratinocytes showing the highest proliferative activity in building up the hair shaft. The common pathogenesis which unites the different etiologies of dystrophic anagen effluvium is a direct insult to the rapidly dividing bulb matrix cells. The abrupt cessation of mitotic activity leads to the weakening of the partially keratinized, proximal portion of the hair shaft, its narrowing and subsequent breakage within the hair canal and shedding. The morphological consequence is dystrophic anagen hair with a tapered proximal end and lack of root sheath (Fig. 13.1a).

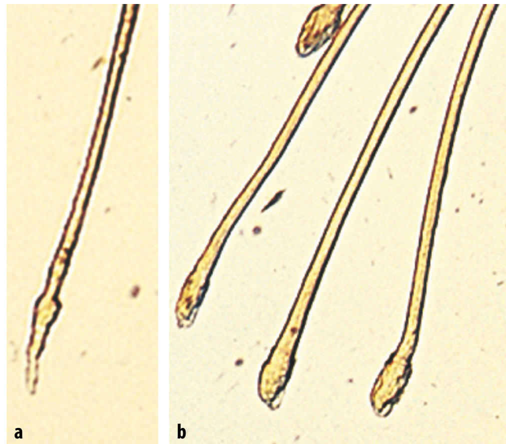


Fig. 13.1a,b **a** Dystrophic anagen hair (light microscopy), **b** telogen hairs (light microscopy)

13.3.2.2 Functional Types of Telogen Effluvium

Telogen effluvium is hair loss that results from increased shedding of hairs from the telogen phase of the hair cycle. An increase in the percentage of follicles in telogen to >20% leads to increased shedding of normal club hairs (Fig. 13.1b).

On the basis of changes in different phases of the follicular cycle, Headington proposed classification of telogen effluvium into five functional types based on changes in different phases of the hair cycle [32]:

1. In *immediate anagen release*, follicles that would normally complete a longer cycle by remaining in anagen prematurely enter telogen. It is a very common form of telogen effluvium, typically occurring after periods of physiologic stress including episodes of high fever. In fever, the pyrogens, basically circulating cytokines, drive the hair follicle keratinocytes into apoptosis initiating catagen with following telogen. Because the shedding is dependent on transition from anagen through catagen and telogen with subsequent release of telogen hairs, hair loss occurs 3–4 months after the inciting event.
2. In *delayed anagen release*, hair follicles remain in prolonged anagen rather than cycling into telogen. When finally released from anagen, the clinical sign of increased shedding of telogen hair will be found. This type of telogen effluvium underlies post partum hair loss.

3. In *immediate telogen release*, hair follicles normally programmed for release of the club hair after an interval of usually 100 days after the end of anagen are prematurely stimulated to cycle into anagen. There is premature teloptosis. This type of telogen effluvium underlies the shedding of hair upon initiation of therapy with topical minoxidil (shedding phase).
4. In *delayed telogen release*, hair follicles remain in prolonged telogen rather than being shed and recycling into anagen. When finally teloptosis sets in, again the clinical sign of increased shedding of club hairs is observed. This process underlies molting in mammals and probably also seasonal shedding of hairs in humans or mild telogen effluvia following travel from low-daylight to high-daylight conditions.
5. Finally, a *short anagen phase* (without synchronization) results in a slight but persistent telogen effluvium in association with decreased hair length: this may occur in hereditary hypotrichosis, ectodermal dysplasia (tricho-dental syndrome), and as an isolated disorder in otherwise healthy children [6]. Far more frequent is acquired progressive shortening of anagen due to androgenetic alopecia (see Sect.13.5).

13.4 Clinical Features

A simple office technique for evaluation of hair loss is to pull gently on the patient's hair (hair pull test). Normally, one can come away with up to five hairs, but with pathologic hair loss this number is increased (positive hair pull). In diffuse hair loss the hair pull test is positive in both the vertex area and margins of the scalp. Diffuse hair loss is further classified by the types of hairs that are shed, in particular whether they are anagen hairs (anagen effluvium) or telogen hairs (telogen effluvium).

13.4.1 Anagen Effluvium

Two types of anagen effluvium are recognized: dystrophic anagen effluvium and loose anagen hair.

13.4.1.1 Dystrophic Anagen Effluvium

Causes for dystrophic anagen effluvium are antineoplastic drugs (chemotherapy-induced alopecia), radiation (radiation-induced alopecia), environmental or occupational exposure to toxins (toxic alopecia), and alopecia areata (see Sect.13.5). All of these, as different as they are, have one thing in common which explains the exceptional phenomenon of anagen effluvium: they stop the reproduction of matrix cells; but, evidently mitotic inhibition alone is not sufficient to force the follicle into catagen, and merely causes it to suspend operations. Presumably, the induction of catagen, normally or under pathologic conditions, is controlled by forces acting through the hair papilla rather than on the follicular epithelium directly.

Chemotherapy-induced alopecia is understood to be the consequence of a direct toxic insult to the rapidly dividing bulb matrix cells of the hair follicle during anagen. With high doses of chemotherapy the hairs may be easily epilated in a week or two shortly followed by diffuse spontaneous hair loss. The usual change in the hair root is quite characteristic and consists of sharp thinning or constriction at which points the hairs simply separate. With lower doses there is only a segmental thinning or narrowing without fracture of the shaft at the point of weakness. When the drug is stopped, the follicle usually resumes its activity in a few weeks, having suffered no more than a temporary arrest in its growth. Another course of the drug produces these changes again. Even when these events are re-enacted many times by repeated courses, hair growth is usually only temporarily inhibited. After the hair has regrown, the telogen count is found to be the same even after repeated episodes of hair loss, showing that the hair cycles are not materially altered. Histologically there is a reduction in the volume of the hair bulb reflecting loss of epithelial cells, nonetheless the hairs continue in anagen. Clearly, chemotherapy-induced dystrophic anagen effluvium differs from telogen effluvium, also in terms of clinical presentation. Since up to 90% of scalp hair is in anagen at a given time, and anagen effluvium is not dependent on the transition from anagen to telogen with subsequent release of telogen hairs, hair loss is copious (80%–90%) and occurs within days to a few weeks of the causative event (Fig. 13.2). Nevertheless, experimental evidence also exists in the literature [9] that the hair follicle may respond to the same insult capable of stopping mitosis with both shedding patterns, i.e., dystrophic anagen effluvium and telogen effluvium. When an arrest of mitotic activity occurs, numerous and interacting factors influence the choice of the shedding pattern: one of these factors is the mitotic activity of the hair follicle at the moment of insult. When the hair is in its phase of highest mitotic rate, the arrest of mitosis causes differentiation to stop, producing a sharp constriction of the hair shaft and, therefore, its fracture. When the hair is in its late anagen phase, in which the mitotic rate is slowing down spontaneously, it simply accelerates its normal way to telogen. Finally, mitotically inactive phases of the hair cycle (catagen and telogen) are not affected. The intensity and duration of the antimitotic insult are also important. The incidence and severity of the hair loss are variable and related to the particular chemotherapeutic protocol. Chemotherapy given at a high dose for



Fig. 13.2 Dystrophic anagen effluvium following chemotherapy

a sufficiently long time may affect all hairs. The scalp is the most common location for hair loss; other terminal hairs are variably affected depending on the percentage of hairs in anagen. The beard, eyebrows, eyelashes, axillary, and pubic hairs may become involved with multiple exposures over a long period. Once the insult is removed, usually regrowth is prompt since normal anagen growth was only temporarily interrupted. Nevertheless, permanent alopecia following chemotherapy with busulfan after bone marrow transplantation has been reported [5, 76], and risk factors included chronic graft-versus-host reaction, prior exposure to X-ray, and older age [79]. Finally, there are circumstances in which telogen effluvium is the more likely to occur. The most common circumstance is androgenetic alopecia. In this condition, anagen duration is diminished and, consequently, the probability that the antimitotic insult strikes the hair close to the resting phase is increased. Synchronization of hair cycles also plays a role. The long duration of anagen is the main factor determining the individuality of the hair cycle in humans. Again, in androgenetic alopecia, the hair cycles tend to synchronize due to the diminished duration of anagen. Even a minor antimitotic insult, therefore, may produce marked hair loss.

Radiation-induced alopecia may either be reversible or permanent. Radiation-induced temporary epilation may be observed following neuroradiologically guided embolization procedures [34]. Permanent alopecia occurs with >30 Gy of deep X-rays, or >50 Gy of soft X-rays [52].

Toxic alopecia from occupational exposure to hazardous chemicals has decreased over the years due to more stringent government regulations. More recently, interest has focused on mild aggressions from toxic metals of the environment. Many heavy metals are capable of disrupting the formation of the hair shaft through covalent binding with the sulfhydryl groups in keratin: thallium, mercury, arsenic, copper, cadmium, and bismuth. A study conducted 1979 in Belgium reported diffuse alopecia related to ingestion of toxic metals in 36 of 78 patients with diffuse alopecia [56]. Toxic metals in abnormal amounts in blood and urine were observed only when >10% of hair bulbs were dystrophic. Copper was involved in 17 alopecias, arsenic in 12, mercury in 5, and cadmium in 2. Copper intoxication was found to be related to ingestion of tap water containing a high concentration of copper salts, presumably from low pH, the presence of chelating agents, or the connection of electrical ground wires to copper water pipes, which caused sufficient flow of electrical current to ionize the metal [56]. Adverse effects related to dental amalgam, including hair loss, have also been the subject of recent attention. In one study [8], mercury levels in blood and urine correlated with the number of amalgam surfaces, indicating the release of mercury from dental amalgam restorations. Since the mercury levels were far below those at which negative health effects would be expected and were similar in patients with complaints self-related to dental amalgam restorations and in healthy control individuals, mercury was not found to be a likely cause of the impaired health reported by the patients. In another study [41], assays of mercury in urine samples of patients with “amalgam illness” indicated that the exposure was far below the levels at which symptoms could be indicated by psychometric tests. Psychologic investigation indicated that the symptoms were psychosomatic. All patients had experienced important psychic traumata in close correlation with the first appearance of symptoms.

Alopecia areata probably represents the most frequent cause of anagen dystrophic effluvium, either localized or diffuse, occurring in the otherwise healthy child (Fig. 13.3) or adult. Alopecia areata is regarded



Fig. 13.3 Dystrophic anagen effluvium in an otherwise healthy child due to alopecia areata

as an organ-specific autoimmune disease, with the hair follicle being the target of autoimmunity. The cytokines generated by a peribulbar lymphocytic infiltrate cause apoptosis of the hair follicle keratinocytes.

13.4.1.2 Loose Anagen Hair

Loose anagen hair, characterized by easily pluckable anagen hairs, is a disorder predominantly described in children. The condition often recedes with age, but can be seen in adulthood, either as a continuation of the disorder that has lingered since childhood, or as late-onset loose anagen hair [74]. Loose anagen hair-like changes have also been associated with acquired immunodeficiency syndrome (AIDS trichopathy) [67]. Patients with late-onset loose anagen hair state that their hair has increased shedding and does not grow as long as it used to. Clinically the hair may show uneven ends. Additionally, there may be variations in hair texture, and the hair is often dry and lack luster.

The diagnosis of loose anagen hair is based on the following criteria [74]: on pull test, painless extraction of more than ten anagen hairs; in the trichogram, >80% of plucked hairs are anagen hairs devoid of sheaths (Fig. 13.4).

Histological studies of scalp biopsy samples have demonstrated abnormal clefting between the internal root sheath and the hair shaft [30], premature keratinization [58], and degeneration of the inner sheath [30]. Also, poor cohesion of the cells of the outer sheath has been described [4]. Ultrastructural studies show longitudinal grooves of the hair shaft. The presence of these alterations supports the hypothesis of some abnormality of the root sheath adversely affecting anchorage of the anagen hair in the follicle.



Fig. 13.4 Loose anagen hair: anagen hairs devoid of root sheaths (light microscopy)

13.4.2 Telogen Effluvium

Most patients with hair loss seen in clinical practice present with telogen effluvium. As telogen hairs have a depigmented bulb, examination of shed or pulled hairs with the naked eye will usually clarify this.

In Kligman's original description [37], telogen effluvium is an acute and diffuse hair loss brought about by a variety of triggers. Clinical experience, however, suggests that chronic telogen effluvium also exists. It is defined as diffuse telogen hair loss that persists >6 months.

13.4.2.1 Acute Telogen Effluvium

Acute telogen effluvium presents as a diffuse, non-patterned hair loss from the scalp that occurs around 3 months after a triggering event, and is usually self-limiting within 6 months by definition.

A host of different triggers have been implicated and identify the cause, e.g., post-febrile, postpartum, psychogenic effluvium, etc. Severe febrile illness, childbirth, accidental trauma or surgical operations with large blood loss, a crash diet, or severe emotional distress are among the most common causes [68].

Hair loss is usually <50% of scalp hair. The diffuse hair loss from the scalp may produce thinning of hair all over the scalp, but frequently manifests with bitemporal recession (Fig. 13.5).

Reassuring patients that they are not going bald, and that the telogen effluvium is temporary is usually sufficient. If the cause is not obvious from the patient's history, iron studies, thyroid function tests, syphilis serology, and an antinuclear antibody titer should be performed [68]. A drug history, and in women in particular a change in the contraceptive pill or hormone replacement therapy should be inquired about, as these are common causes of telogen effluvium related to androgenetic alopecia (see Sect. 13.5).

The literature on the subject of *psychogenic hair* loss has been more confounding than helpful. The presence of emotional stress is not indisputable proof of its having incited the patient's hair loss. The relationship may also be the inverse. Nevertheless, recent studies suggest that women who experience high stress are more likely to experience hair loss [83]. Moreover, in a murine model, experimental stress has been shown to inhibit hair growth, indicating the existence of a brain–hair follicle axis [2].

13.4.2.2 Chronic Telogen Effluvium

Diffuse shedding of telogen hairs that persists >6 months either represents a primary disorder and is



Fig. 13.5 Chronic telogen effluvium: bitemporal thinning

then a diagnosis of exclusion, or is secondary to a variety of systemic disorders [70]: iron deficiency, other dietary deficiencies (protein-calorie malnutrition, zinc deficiency) [27], thyroid disease [17], other metabolic diseases (chronic renal or liver failure, advanced malignancy, pancreatic disease and upper gastrointestinal disorder with malabsorption), systemic lupus erythematosus [82], other connective tissue disorders [36], HIV infection [45], and drug-induced telogen hair loss [11, 42, 63, 73] (Table 13.1). Apart from iron deficiency as a cause of chronic diffuse hair loss, all others are less common, although the literature concerning iron deficiency remains controversial. Iron deficiency has been reported in the majority of women presenting with diffuse hair loss [64, 65], but this probably has been overestimated. More recent data suggest that in most women with chronic telogen effluvium, no direct relationship between low serum ferritin levels (≥20 μg/l) and hair loss exists [3, 69].

While chronic telogen effluvium may be triggered by an acute telogen effluvium, in *primary chronic telogen effluvium* no specific trigger is evident. It predominantly affects women, while men with short hair tend not to notice increased hair shedding. The presentation of this type of diffuse hair loss tends to be distinctive, and was first described in detail by Guy and Edmundson as "diffuse cyclic hair loss in women" [28], and revived by Whiting in 1996, who additionally characterized the histopathologic features [81]. The typical patient is a vigorous otherwise healthy woman between 30 and 60 with a full, thick head of hair. On examination there is some bitemporal recession and a positive hair pull test equally over the vertex and occiput. There is no widening of the central part, as is common in androgenetic alopecia. Nevertheless, patients are adamant that they previously had more hair and are distressed by the prospect of going bald. Many frequently bring large balls of hair for inspection (Fig. 13.6), but despite this do not show any



Fig. 13.6 Hair ball brought in by patient with chronic telogen effluvium

obvious balding. The condition tends to run a fluctuating course, at times reflecting seasonal periodicity in the growth and shedding of hair with a maximal proportion of telogen hairs at the end of summer and the beginning of autumn [19]. In the long run the disorder appears to be self-limiting. It is important to reassure patients that this condition represents exaggerated shedding rather than actual hair loss. It has been proposed that this disorder may be due to synchronization phenomena of the hair cycle [28], shortening of the anagen phase [32], or premature teloptosis [60]. As often happens in skin diseases in women, cosmetics are often thought to be the cause. Shampoos and hair colorants are blamed. While the absence of effects of shampoos on hair loss rates has been demonstrated [39], telogen effluvium after allergic contact dermatitis of the scalp has been reported [75].

13.4.3 Quantitating Hair Loss

Reliably assessing the actual shedding of hair is a crucial diagnostic point in trichological practice. To fulfill office requirements, the test should be easy, non-invasive, and

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Table 13.1 Drugs responsible for diffuse hair loss (selection)

Dystrophic anagen effluvium	
Inhibition of mitosis (dystrophic anagen effluvium): cytostatic agents	
Cytostatic agents which usually do cause hair loss:	Adriamycin
	Docetaxel
	Daunorubicin
	Paclitaxel
	Etoposide
	Ifosfamide
	Irinotecan
	Vindesine
	Cyclophosphamide
	Vinorelbine
	Epirubicin
	Topotecan
Cytotoxic agents which sometimes cause hair loss:	Amsacrine
	Vincristine
	Cytarabine
	Vinblastine
	Bleomycin
	Lomustine
	Busulfan
	Thiotepa
	5-Fluorouracil
	Gemcitabine
	Melphalan
Cytotoxic agents which unusually cause hair loss:	Methotrexate
	Procarbazine
	Carmustine
	6-Marcaptopurine
	Mitroxantrone
	Streptozotocin
	Mitomycin C
	Fludarabine
Dystrophic anagen effluvium (*continued*)	
Inhibition of mitosis (dystrophic anagen effluvium): cytostatic agents (*continued*)	
Cytotoxic agents which unusually cause hair loss:	Carboplatin
	Raltritrexed
	Cisplatin
	Capecitabine
Telogen effluvium with known or assumed mechanism:	
Interference with keratinization process in the hair follicle: retinoids	Vitamin A (>50,000 I.E. daily)
	Acitretin
	Isotretinoin
Interference with blood flow in follicular papilla: anticoagulants	Heparin
	Warfarin
Interference with cholesterol synthesis: lipid-lowering agents	Fibrates (Clofibrate, Bezafibrate, Fenofibrate)
	Lovastatin
Complexation of zinc (thiol moiety): ACE inhibitors	Captopril
	Enalapril
Interference with thyroid metabolism: thyrostatics and others	Propylthiouracil
	Levothyroxine
	Amiodarone (anti-arrhythmic)
	Lithium (antipsychotic)
Androgen effect: androgens, anabolics and progestins with androgenic effect	Mesterolone
	Testosterone
	Danazol
	Nandrolone
	Stanozolol
	Norethisterone
	Levonorgestrel
	Tibolone

Table 13.1 *(continued)* Drugs responsible for diffuse hair loss (selection)

Telogen effluvium with known or assumed mechanism (*continued*)**:**	
Aromatase inhibition: aromatase inhibitors	Letrozole
	Anastrozole
	Formestane
Cytokine effect: interferons	Alpha interferon
	Gamma interferon
Telogen effluvium with unknown mechanism (in order of indications):	
Blood-pressure-lowering agents (beta-blocking agents):	Acebutolol
	Nadolol
	Atenolol
	Pindolol
	Labetalol
	Propranolol
	Metoprolol
Topical beta-blocking agents for therapy of glaucoma:	Betaxolol
	Timolol
	Levobunolol
Analgesics/non steroidal anti-inflammatory agents:	Acetaminophen
	Piroxicam
	Ibuprofen
	Indomethacin
	Ketoprofen
	Penicillamine
	Naproxen
	Gold and gold compounds
Psychotropic agents/anti-depressants:	Amitriptyline
	Haloperidol
	Desipramine
	Imipramine
	Doxepin
	Nortriptyline
	Fluoxetine
	Trimipramine

Telogen effluvium with unknown mechanism (in order of indications) (*continued*)**:**	
Antiepileptics	Carbamazepine
	Paramethadione
	Clonazepam
	Phenytoin
	Ethotoin
	Trimethadione
	Mephenytoin
Antiepileptics	Valproic acid
Antibiotics/ tuberculostatics:	Thiamphenicol
	Isoniazid
	Ethambutol
	Gentamicin Nitrofurantoin
Varia	Chloroquine, hydroxychloroquine (antimalarials)
	Albendazole, mebendazole (anthelminthic agents)
	Cimetidine, famotidine, ranitidine (antacids)
	Allopurinol (uricostatic agent)
	Sulfasalazine (antiphlogistic/ sulfonamide)
	Bromocriptine (prolactin inhibitor/ anti Parkinson agent)
	Levodopa (anti-Parkinson agent)
	Halothane (inhalation anesthetic)

not time-consuming. Many methods have been proposed, but all need standardization. The hair pull test has been found to be a poorly sensitive method, while telogen percentage in the trichogram does not correlate with severity of hair loss [26]. While the daily hair count is a cumbersome procedure, it has been proposed that the wash test is probably the best method to adopt [26]. In the wash test, the patient, 5 days after the last shampoo, washes the hair in the sink with its drain covered by gauze. The hairs entrapped in the gauze are then counted [48]. In one study assessing hair shedding in children, the wash test proved to be reliable, with a cutoff point of normality close to 11, and wash test values increasing with age [59]. More so, measurement of the effects of treatment needs to be quantified reliably. The method should be more sensitive than the wash test, and capable of analyzing relevant parameters of hair growth; namely, hair density, hair diameter, hair growth rate, and anagen/telogen ratio. For this purpose, a technique has been developed that combines epiluminescence microscopy with automatic digital image analysis (TrichoScan) [33].

13.5 Differential Diagnosis

The most important differential diagnoses of diffuse telogen hair loss include androgenetic alopecia and psychogenic pseudoeffluvium. There is considerable overlap between the two, further complicating differential diagnosis, especially in women [77]. Far less common is diffuse alopecia areata.

13.5.1 Androgenetic Alopecia

Androgenetic alopecia is the most common cause of hair loss in men (Chap. 9) and in women (Chap. 10). It is characterized by hair loss in a distinctive pattern that differs between men (male pattern hair loss) [29, 46] and women (female pattern hair loss) [43]. In the early stages of androgenetic alopecia the pattern may not be apparent, and patients may complain of diffuse hair loss. This presentation is far more common in women, and is sometimes observed in children of both sexes with a prepubertal onset of androgenetic alopecia [7]. This can pose diagnostic difficulties.

13.5.1.1 Female Pattern Hair Loss

Recent literature suggests that patterned hair loss may have different mechanisms in men and in women [47]. Because the androgen dependence of hair loss in all women with this type of alopecia has not been sufficiently demonstrated, and it has been observed in the absence of circulating androgens [51], the term female pattern hair loss has been proposed to replace androgenetic alopecia when applied in women [49, 50]. Nevertheless, female pattern hair loss shares with androgenetic alopecia the histolopathologic feature of hair follicle miniaturization. A terminal-to-vellus ratio of <4:1 on a horizontally sectioned 4-mm scalp biopsy is diagnostic of androgenetic alopecia, while a ratio >7:1 suggests chronic telogen effluvium [80].

13.5.2 Psychogenic Pseudoeffluvium

Patients seeking advice for hair loss are not necessarily balding. When they have normally dense scalp hair, and absence of any convincing evidence of hair loss, they are regarded as suffering of "imaginary hair loss" or psychogenic pseudoeffluvium. In these cases thought should be given to underlying psychological disorders.

13.5.2.1 Alopeciaphobia

Mild instances of *alopeciaphobia* [37] are common in connection with depressive disorder.

13.5.2.2 Telogen Mania

Some extremely hair-conscious patients are capable of fierce fits of hair brushing, *telogen mania*, which is perhaps a modified form of obsessive-compulsive disorder or trichotillomania [37].

13.5.2.3 Delusion of Alopecia/Body Dysmorphic Disorder

Finally, the physician should be aware of the potential seriousness of *delusion of alopecia* and of *body dysmorphic disorder* [18], both nearly psychotic states.

13.5.3 Alopecia Areata

Alopecia areata (see Chap. 15) is an immune-mediated form of hair loss, which commonly presents as localized patches of bald scalp. An as yet unidentified trigger stimulates an autoimmune lymphocytic attack on the hair bulb. The inflammation is specific for anagen hairs and causes anagen arrest.

13.5.3.1 Diffuse Alopecia Areata

With a proportion of 2%, diffuse alopecia areata is the least common clinical type of alopecia areata, and is largely confined to the >40 age group [44]. It lacks the characteristic patches of alopecia and instead demonstrates widespread thinning that is severe and rapidly progressive, often evolving to total hair loss. The patient with diffuse alopecia areata may also complain of rapid graying of hair (Fig. 13.7).

13.5.3.2 Chronic Diffuse Alopecia Areata/Diffuse Alopecia with Stem Cell Folliculitis

Chronic diffuse alopecia areata is particularly rare. Patients present with profound hair loss, but often are not actively shedding. The alopecia may have a slightly reticular pattern.

Where no patch of alopecia coexists as a clue to the diagnosis, a biopsy is usually required to establish the identification. Optimal specimens include two 4-mm punch biopsy specimens from the vertex submitted for horizontal and vertical embedding [22].

The histologic features depend on the stage of the disease, and biopsy specimens of clinically active alopecia areata show peribulbar lymphocytic infiltrates around anagen follicles [31]. Especially in biopsy specimens from long-standing areas of alopecia areata with an increased number of telogen follicles and follicular miniaturization, the histology is sometimes equivocal, since a light perifollicular lymphocytic infiltrate can be a non-specific histologic finding. In this context, it is not clear whether Kossard's *diffuse alopecia with stem cell folliculitis* [38] represents chronic diffuse alopecia areata or a distinct entity. Further studies to clarify this issue are warranted.



Fig. 13.7 Diffuse alopecia areata with graying of hair

A response with hair regrowth to oral prednisolone in doses >0.5 mg/kg for 3–4 weeks with subsequent tapering is sometimes required to establish the diagnosis of diffuse alopecia areata [68].

13.6 Treatment

Management and prognosis of diffuse hair loss depend on the cause and underlying pathomechanism in its relation to the hair growth cycle.

Most acute telogen effluvia, particularly those due to acute-onset physiologic events (e.g., postfebrile, postpartum), as well as mild seasonal telogen effluvium, and the shedding phase observed upon initiation of topical minoxidil treatment are self-limiting and will undergo normal reversal.

The cause of chronic telogen effluvium may be multifactorial and difficult to establish. Systemic diseases known to cause telogen effluvium, such as iron deficiency, thyroid dysfunction, systemic lupus erythematosus, and syphilis, need to be systematically excluded or treated. Drugs known to cause hair loss, such as anticoagulants (heparin, warfarin), oral retinoids (acitretin, isotretinoin), interferon, agents with antithyroid action (carbimazole, propylthiouracil, amiodarone), hypolipidemic agents (fibrates), colchicine, antimetabolites (methotrexate, azathioprine, cyclophosphamide), and hormones with pro-androgen action (norethisterone, levonorgestrel, tibolone) should be discontinued unless they are essential for the patient. Finally, in young women, the diet should be addressed. If anorexia nervosa/bulimia is suspected, the aid of a psychiatrist should be sought; in other cases the informed patient will be happy to abandon any dietary culprit.

Differential diagnosis may be complicated by considerable overlap, especially with androgenetic alopecia; for instance, postpartum effluvium after which the hair does not necessarily return to the same antepartum texture and length. In these cases the addition of topical minoxidil to the treatment regimen is usually helpful. Synchronization phenomena of hair cycling, also on a seasonal basis, seem to be more pronounced in patients with androgenetic alopecia, since with a shorter anagen phase a greater proportion of hair follicles will synchronize.

Recommendations for treatment of primary chronic telogen effluvium are scanty, and include topical or systemic corticosteroids [28], topical minoxidil [60], and dietary supplements on the basis of millet extract [1], pantothenic acid, biotin [23], their combination [20], and combinations of L-cystine, medicinal yeast and pantothenic acid ("CYP-complex"). The rationale for the use of L-cystine is based on the biochemistry of cys-

tine metabolism, clinical observations in disorders of cystine metabolism and cystine deficiency, and results of animal and human studies. In the 1960s, the role of L-cystine in the production of wool was investigated, and it was found that enrichment of even what appeared to be a normal diet with sulfur-containing amino acids increased wool production in sheep [24, 25, 62]. When considering which dietary supplements could be used to improve hair growth in humans, L-cystine was therefore a candidate. In the early 1990s studies on the effect of dietary supplements containing L-cystine in combination with B-complex vitamins and medicinal yeast, a rich natural source of B-complex vitamins, were published and showed improvements in the trichogram, in hair swelling as a criterion for hair quality, and in the tensile strength of the hair fiber [12, 55]. One double-blind, placebo-controlled study performed with the TrichoScan technique in 30 otherwise healthy women suffering from telogen effluvium demonstrated that a dietary supplement with "CYP-complex" increased the anagen hair rate within 6 months of treatment, while placebo did not [40]. The supplement did not have any effect on terminal hair counts, hair density, and cumulative hair shaft diameter, and thus would not seem to be indicated for treatment of alopecia due to cycle shortening, such as androgenetic alopecia. Since synchronization phenomena tend to complicate the course of alopecias due to anagen shortening, *adding* a CYP-complex-based dietary supplement to the treatment with minoxidil may nevertheless be beneficial. It has been shown in whole hair follicle cultures that minoxidil not only increases the incorporation of thymidine as a marker of cell division, but also leads to an increased uptake of cysteine by the hair follicle [13]. Most importantly, women with chronic telogen effluvium need to be reassured that it represents exaggerated shedding rather than actual hair loss and that the shed hair is mostly being replaced; therefore, the risk of total baldness is remote [47].

Finally, the issues of psychogenic effluvium and of overvalued ideas in relation to the condition of the hair are not always easy to resolve; however, it is important to control stress as a complication of hair loss or fear of hair loss. For this purpose strong psychological support is essential to help limit patient anxiety, and patients need to be educated about the basics of the hair cycle. Information about the hair cycle can be useful to explain how an effluvium not related to cycle shortening (as in androgenetic alopecia) generally precedes new regrowth, and why considerable patience is required for effective cosmetic recovery.

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Summary for the Clinician

Diffuse hair loss is a common complaint, and it is paramount that the physician addresses this symptom seriously. The diagnosis can usually be established with a history, particularly focusing on the chronology of events, examination of the scalp, pattern of hair loss, results of a pull test, examination of the bulbs of the shed hairs, and a few pertinent screening blood tests. In chronic cases a scalp biopsy may be required. Once the diagnosis has been established, treatment appropriate for that diagnosis is likely to control the hair loss except in chronic telogen effluvium. Patients with chronic telogen effluvium, as well as patients with overvalued ideas with respect to the condition of their hair can, however, be handled satisfactorily by unpatronizing sympathy from a knowledgeable and caring physician and firm exposition of the dynamics of hair growth.

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Chapter 14

Hair Loss in Children

14

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Synonyms

hair loss in neonates and children, hair shaft defects, genotrichoses, congenital alopecia, hypotrichia, atrichia, non-scarring alopecia, scarring alopecia

Key Features

- Hair loss in children comprises a broad spectrum of disorders.
- Hair shaft defects with increased fragility simulate hair loss and should be considered in children with abnormal hair growth.
- Hair loss may present as localized, patchy or as diffuse alopecia.
- Close inspection of the scalp helps to further differentiate between non-scarring alopecia and scarring alopecia.
- In children, a thorough clinical examination is mandatory in all forms of hair loss to detect associated anomalies or diseases.
- Interdisciplinary work up is often required in children with hair loss.
- Careful guidance of the parents is needed to support coping with the diseases.

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Hair loss in neonates and children is frequently regarded as an alarming symptom by parents and pediatricians. A careful work up and a critical consideration, as to whether physiological or pathological causes are responsible, are highly important for clarification of the etiology. Age of onset is a helpful tool to sort the diagnostic approach considering main differential diagnoses of hair loss in childhood (Table 14.1). After a close clinical inspection hair loss can be further classified according to its clinical pattern (Table 14.2). However, basic knowledge of hair follicle development, hair biology and physiology is important for critical analysis and classification of the different conditions.

Hair follicles begin their development around the 14th gestational week and show rapid growth, with hair shafts visible by the 18th week [43]. Lanugo hair (fine, unpigmented, unmedullated, up to several centimeters in length) covering the scalp with development in a cephalocaudal direction covers possibly the whole fetus by the end of the second trimester. *Physiological shedding* of lanugo hair occurs during the 7th to 8th month of intrauterine life and is rapidly replaced by vellus hair on the body and terminal or vellus hair on the scalp [7, 20]. This transition wave may be delayed in the occipital area at 2–4 months postpartum explaining the circumscribed alopecia on the occiput of newborns at this age. Total follicle density of the scalp has been reported to be 1135 hairs/cm² at birth; as the body surface increases there is a decrease in the actual density of follicles with increasing age. Scalp terminal hair shows synchronous

Table 14.1 Main differential diagnoses of hair loss in childhood, subdivided according to age at onset [56]

Age group (years)		
1–3	4–11	12–18
Genetic hair shaft defects	Autoimmune-inflammatory hair loss	Autoimmune-inflammatory hair loss
Congenital hypo-, atrichia and aplasia	Acquired hair shaft defects	Acquired localized non-scarring hair loss
Scalp infection (rare)	Scalp infection	Hormonal dysregulation androgen alopecia
Autoimmune-inflammatory hair loss (rare)	Acquired diffuse non-scarring hair loss	Androgenetic alopecia
	Congenital hypotrichia (rare)	Acquired diffuse non-scarring hair loss
		Scarring alopecia (rare)

Table 14.2 Classification of hair loss according to its clinical pattern[a] [56]

Hair shaft defects simulating hair loss			
Genetic	Trichorrhexis nodosa Monilethrix Pseudomonilethrix Pili torti Netherton Syndrome Menkes Syndrome Trichothiodystrophy Ectodermal dysplasia	**Acquired**	Weathering Bubble hair Trichorrhexis nodosa
Localized hair loss with non-scarring alopecia	Alopecia areata Tinea capitis, folliculitis/pyodermia Trichotillomania Traction alopecia Triangular alopecia Loose anagen hair	**Diffuse hair loss with non-scarring alopecia**	Telogen effluvium Alopecia areata diffusa, totalis or universalis Loose anagen hair Congenital hypo- and atrichia
Localized hair loss with scarring alopecia	Congenital aplasia cutis Deep fungal, bacterial or viral infection Physical, chemical or mechanically induced scarring alopecia	**Diffuse hair loss with scarring alopecia**	Keratosis follicularis spinulosa decalvans Pseudopelade Brocq

[a]Most frequent disorders are presented.

hair growth activity until the end of the first year of life, with *physiological increased shedding* at the end of this period due to individual cycling and asynchronous hair growth activity of each hair follicle.

Pathological hair loss rarely occurs during the first year of life but may be a leading symptom of *congenital* diseases. For the classification of pathological hair loss in children, three major groups should be differentiated: hair shaft defects simulating hair loss, localized hair loss, and diffuse hair loss.

14.1 Hair Shaft Defects Simulating Hair Loss

Hair shaft defects in children may cause fractures due to increased fragility of the hair shafts or they may present as irregularities along the hair shafts without increased breakage. Increased fragility may simulate hair loss and is found in, for example, trichorrhexis nodosa, congenital or acquired monilethrix, pseudomonilethrix, and pili torti. These hair shaft anomalies are either associated with other clinical features or are isolated. Hair defects found in Netherton disease, Menkes disease or trichothiodystrophy present as specific syndromes of variable expression. In most cases, there is no causal therapy but genetic counseling of parents is necessary. However, defects of the hair shaft may also be acquired, as in acquired trichorrhexis nodosa, weathering or bubble hair. Reduction of repeated trauma to the hair shaft should result in normal regrowth of hair. Light microscopy of hairs longitudinally embedded in hair mount is a helpful diagnostic tool to identify the underlying hair shaft defect (Table 14.3).

14.1.1 Trichorrhexis Nodosa Congenita

Synonyms

trichorrhexis nodosa syndrome, Pollitt syndrome OMIM 275550, argininosuccinic aciduria OMIM 207900, biotinidase deficiency OMIM 253260

Table 14.3 Differential diagnosis of hair shaft defects with increased fragility in children (**A**): light microscopy and characteristic findings in longitudinally embedded hair in hair mount. (*EM* Electron microscopy, *HI* Histology, *LM* light microscopy, *PLM* polarizing light microscopy, *TRG* trichogram) *see next page*

A Hair shaft defects with increased fragility

Hair defect	Typical findings
Trichorrhexis nodosa	LM: Fracture with individual cortical cells and their fragments splaying out, resembles two brushes, whereby ends are pushed together
Monilethrix	LM: Uniform elliptical nodes and intermittent constrictions, so-called internodes, along the hair shaft
Pili torti and pili torti with copper deficiency in Menkes disease	LM: Closely grouped twists of flattened hair, twists are each 0.4–0.9 mm in width occurring in groups of 3–10 at irregular intervals along the shaft
Bamboo hair in Netherton syndrome	LM: Typical nodes resembling bamboo joints on longitudinal embedded hair, “cup portion” (proximal part), “ball portion” (distal part)
Trichothiodystrophy	PLM: Tiger-tail pattern LM: Irregular, slightly undulating contour, trichorrhexis-nodosa-like fractures with less release of individual cortical cells and clean, transverse fractures, trichoschisis
Ectodermal dysplasia	LM: Unspecific findings, pili torti may occur; HI: reduced number and hypoplasia of hair follicles and other appendage organs (sweat glands, sebaceous glands, etc.)
Weathering	LM: Bubble-like areas in the hair shaft (bubble hair), typical trichorrhexis nodosa fractures (see above), clean, transverse fissure or fracture through the hair shaft (trichoschisis), a shaft splinted in part by an intact cuticle, classic greenstick fracture (trichoclasis), longitudinal splitting of the hair shaft at its distal end leads to the common split ends (frizzies or trichoptilosis).

Table 14.3 (*continued)* Differential diagnosis of hair shaft defects without increased fragility in children (**B**): light microscopy and characteristic findings in longitudinally embedded hair in hair mount. (*EM* Electron microscopy, *HI* Histology, *LM* light microscopy, *PLM* polarizing light microscopy, *TRG* trichogram)

B Hair shaft defects without increased fragility	
Hair defect	Typical findings
Pili annulati (syn.: ringed hair, pili anulati)	LM: Alternating bright and dark bands along the hair shaft. The bright appearance of the bands is due to air-filled cavities within the cortex that scatter the light. The colors of the bands are reversed when seen with reflected light. (Clinically, banding is seen only in blond or lightly pigmented hair)
Pseudo pili annulati	LM: With transmitted unpolarized light, variations in fiber diameter due to twisting of the oval hair about its long axis are found (the internal structure is entirely normal). PLM: with crossed polarizers and retardation plate, alternating segments of color, i.e., a blue segment followed by a yellow segment are found. (Clinically, banding is seen only in certain positions in blond hair)
Woolly hair	LM: Ovoid or elliptical cross-sections, 180° axial twisting of the hair shaft. Anagen hair bulb is commonly lacking a root sheath, but anagen:telogen ratio is normal. Weathering, trichorrhexis nodosa or lacking of cuticles may be found
Pili trianguli et canaliculi (syn. : uncombable hair, spun glass hair, cheveux incoiffable, Struwelpeter)	LM: May be normal. PLM: Changing alignment of hair shafts EM: Longitudinal grooves and triangular or kidney-shaped cross-sections
Pili bifurcati	LM: Hair shaft separates to form two parallel branches, each vested with a complete circumferential cuticle, then the branches fuse again to form a single hair shaft. Splitting and fusing occurs within irregular intervals along the hair
Pili multigemini	Biopsy of the scalp: two to eight matrices and dermal papillae with all hair shafts emerging from one single pilosebaceous canal. Each hair is formed by a single branch of dermal papilla which is surrounded by all layers present in normal follicle except for the outer root sheath cells
Twisted and rolled body hairs with multiple, large knots	LM: Central sticking and knotting of numerous hairs, resulting in one large knot
Acquired progressive kinking of the hair	Clinically, tight, short and curly hair in an otherwise normal scalp appears in circumscribed regions, usually in the frontal and temporal areas with an unruly and rough appearance. Occasionally, all scalp hair may be involved. Affected hairs may be thinner or coarser than in the unaffected scalp regions and hair color darker than normal

14.1.1.1 Introduction

Trichorrhexis nodosa is not specific for a disease, but represents an important diagnostic clue to a possible underlying metabolic disorder. In congenital trichorrhexis nodosa, the hair shaft fragility is often the only abnormal clinical feature. Occasionally, other ectodermal defects can be associated.

14.1.1.2 History

In 1952, Rousset reported about a family with trichorrhexis nodosa and associated defects of teeth and nails [70]. Later on in 1958, Allan and co-workers discovered the association to argininosuccinicaciduria [70]. The term “nodosa” is used primarily for historical reasons. It refers to the node which is sometimes seen with the naked eye at the site of this defect.

14.1.1.3 Epidemiology

Trichorrhexis nodosa is the most common defect of the hair shaft. In general, trichorrhexis nodosa is often found in patients complaining of increased fragility of hairs.

14.1.1.4 Pathogenesis

Trivial trauma to the hair shaft and an inherent weakness of the hair shaft result in trichorrhexis nodosa congenita. The earliest observed change is a localized loss of cuticle cells. The exposed cortical fibers later separate and fray, causing a nodular swelling of the hair shaft. Trichorrhexis nodosa congenita without associated defects is rare. In addition, it may also appear in genetic syndromes such as Netherton syndrome, Tay syndrome, Basex-Dupré-Christol Syndrome and Menkes disease. Trichorrhexis nodosa syndrome, also called Pollitt syndrome, is a form of non-photosensitive trichothiodystrophy. Trichorrhexis nodosa also occurs in metabolic disorders such as biotin and zinc deficiency, or in argininosuccinicaciduria, an autosomal-recessive disorder of the urea cycle. Urea cycle disorders are characterized by the triad of hyperammonemia, encephalopathy, and respiratory alkalosis. Trichorrhexis nodosa has been recorded in hypothyroidism [55].

14.1.1.5 Clinical Features

In trichorrhexis nodosa congenita, the hair often appears normally thick and long at first, but becomes fragile in the first year. The abnormal fragility becomes evident as the hair breaks, leaving variable lengths of broken hair and even partial alopecia. Trichorrhexis nodosa is also found in infants with argininosuccinicaciduria. The onset of symptoms of argininosuccinicaciduria occurs during the first weeks of life. Features include mental and physical retardation, convulsions, episodic unconsciousness, liver enlargement, skin lesions, and dry and brittle hair showing trichorrhexis nodosa microscopically and fluorescing red. In comparison to classic cases, variant cases of argininosuccinate lyase deficiency and argininosuccinic acid synthetase deficiency have been reported. In affected individuals, symptoms may present at birth, within the first months until the second year of life. Lethargy, seizures, respiratory distress at birth or gradual onset of physical, mental retardation, hepatomegaly and ataxia vary depending on the clinical form of argininosuccinicaciduria [22]. Laboratory testing reveals acidosis, hyperammonemia, low serum arginine, elevated serum and urine citrulline and argininosuccinic acid. The hair defect may also be present in biotinidase deficiency, an inborn or acquired error of biotin uptake [107]. In zinc deficiency, clinical features resemble those of acrodermatitis enteropathica [87]. However, other syndromes including ectodermal defects are occasionally associated [49].

14.1.1.6 Pathology

In light microscopy, individual cortical cells and their fragments are splayed-out. The defect resembles two brushes with their ends pushed together (Fig. 14.1a,b).

14.1.1.7 Differential Diagnosis

In trichorrhexis nodosa, acquired forms should be differentiated from congenital forms and associated features. Mainly, trichorrhexis nodosa is acquired and traumatic cosmetic procedures are identified. On clinical inspection, in trichorrhexis invaginata multiple, small nodules are seen along the hair shaft as in trichorrhexis nodosa. To separate trichorrhexis invaginata from trichorrhexis nodosa, embedding of the hair shaft in hair mount will reveal the typical features of bamboo hair.

14.1.1.8 Treatment

In trichorrhexis nodosa, mild cosmetic procedures are recommended to decrease trauma of fragile hair. In argininosuccinase deficiency, a low-protein, arginine-supplemented diet may reverse hair shaft fragility. Early treatment of partial argininosuccinate lyase deficiency may result in normal intellectual and psychomotor development. In biotin deficiency 5 mg biotin per day and in zinc deficiency supplementation of, e.g., 40 mg zinc daily may resolve clinical symptoms [87, 107]. In the case of hypothyroidism, substitution is mandatory.

14.1.2 Monilethrix

Synonyms
Beaded hair OMIM 158000 and 252200

14.1.2.1 Introduction

Monilethrix is a rare, hereditary hair shaft anomaly in which affected fragile hairs have a unique beaded morphology.

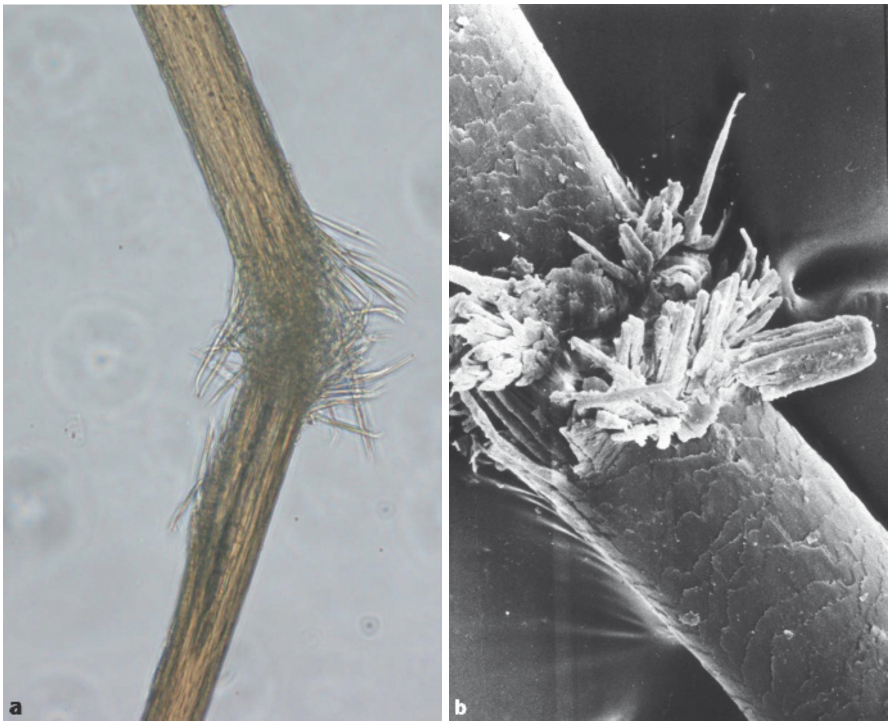


Fig. 14.1a,b Trichorrhexis nodosa resembles two brushes with their ends pushed together (**a** light microscopy; **b** scanning electron microscopy)

14.1.2.2 History

In 1879, Walter Smith described a rare nodose condition of the hair, later known as monilethrix. Due to its distinct morphology resembling a pearl necklace the name derived from the Latin word "monile" (necklace) and the Greek word "thrix" (hair).

14.1.2.3 Epidemiology

Expression of monilethrix is variable: in mild cases, dystrophic hair may be confined to the occiput but more severely affected individuals have near total alopecia. Extensively affected kindred with a pattern of dominant inheritance have been reported [50]. However, some families might have a recessive form of the disorder [83].

14.1.2.4 Pathogenesis

Monilethrix, an autosomal-dominant human hair disorder, is caused by mutations in three type II hair cortex keratins and chromosome 12 q13 [89]. The three hair keratin genes encode the type II hair keratins Hb1, Hb3, and Hb6, which share a completely identical α-helical rod domain and, in line with the ultrastructurally observed disease symptoms, are all expressed in the hair cortex [50]. Rare cases of the disease with non-vertical transmission have now been found to overlap with localized autosomal-recessive hypotrichosis. The underlying gene, desmoglein 4, belongs to the desmosomal cadherin superfamily and is also expressed in the cortex of the hair follicle [83].

14.1.2.5 Clinical Features

Vellus hair is usually present at birth but is soon replaced by dry, brittle and lusterless moniliform hairs. The beaded hair emerges from keratotic follicular papules, breaks spontaneously almost flush with the scalp or obtains a maximal length of 0.5–2.5 cm leading to various degrees of alopecia. In the mildest form, the disease involves only the occiput and the nape of the neck, but in its severe form, the entire scalp, hair of eyebrows and eyelashes, facial pubic and axillary hair, and the hair of the arms and legs may also be affected. Follicular keratosis is associated in affected areas, predominantly on the scalp. In rare cases nail defects (koilonychia), cataract or mental retardation have been found in children with monilethrix [29] (Fig. 14.2).



Fig. 14.2 Monilethrix in a 16-year-old girl. Typical finding of erythematosus papules, follicular keratosis and broken off hairs with various length in the occipital region

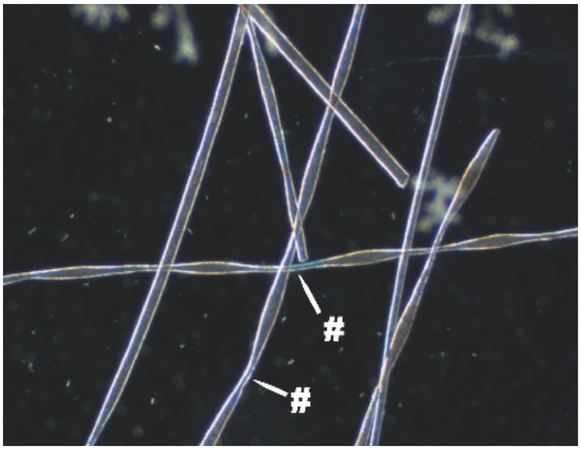


Fig. 14.3 Monilethrix: Uniform regular nodes and intermittent constrictions (internodes #) along the hair shaft are found in light microscopy

14.1.2.6 Pathology

Light polarizing microscopic examinations reveal characteristic uniform nodes and intermittent constrictions (internodes) along the hair shaft. Hairs show regularly spaced fusiform, spindle-shaped or elliptical swellings. The nodes are the normal diameter of the shaft and the internodes represent atrophic parts. Trichorrhexis with broken-off ends may also be seen due to increased fragility of the hair (Fig. 14.3).

14.1.2.7 Differential Diagnosis

Pseudomonilethrix and pili torti should be considered as differential diagnoses. Mainly developing from the age of 6–8 years on, these hair shaft anomalies present mostly without total alopecia, with brittle, fragile hair varying in length from 1 to 4 cm over the occiput and from 10 to 12 cm over areas less exposed to friction. In addition, their features in light microscopy differ to those seen in monilethrix. In pseudomonilethrix, the nodes are irregularly spaced and the internodes represent the normal hair shaft caliber. In pili torti, twists with an angle at about 180° along the hair shaft are found.

14.1.2.8 Treatment

Avoidance of hair trauma is a major principle in the management and counseling of the patient. However, oral acitretin may improve clinical conditions, but symptoms recur after discontinuation [47]. Occasionally, regrowth of apparently normal hair may occur at the time of puberty or during pregnancy [12].

14.1.3 Pseudomonilethrix

Synonyms
pseudo-monilethrix OMIM 177750

14.1.3.1 Introduction

Pseudomonilethrix has been classified in three different types: I, familiar pseudomonilethrix of Bentley-Phillips (autosomal-dominant inheritance); II, acquired pseudomonilethrix in dysplastic disorders with hair fragility (inheritance profile depending on the dysplastic disorder); and III, iatrogenic pseudomonilethrix [30].

14.1.3.2 History

It was first described by Bentley-Phillips and Bayles [12] in 1973 and clinically affects the whole scalp as a generalized hypotrichosis or just the occipital area. The

term was chosen to indicate the resemblance to classical monilethrix.

14.1.3.3 Epidemiology

Pseudomonilethrix is a rare dysplastic disorder of the hair shaft that is inherited as an autosomal-dominant trait with high penetration but variable expressivity.

14.1.3.4 Pathogenesis

Pseudomonilethrix, a developmental hair shaft defect, is characterized by irregular nodes along the hair shaft, with fragility and breakage of hair resulting in partial baldness. Due to spontaneous breakage of the hairs, varying degrees of alopecia only involving the scalp are seen. However, artifactual induction should be excluded. As yet no specific pathogenetics are known.

14.1.3.5 Clinical Features

Pseudomonilethrix may start in the first months of life, although, in some cases, it does not become apparent until childhood. Hair is dry, brittle, irregular in length and difficult to groom. No follicular papules can be seen on physical examination. In children with acrodermatitis enteropathica and reduced hair density pseudomonilethrix may be found [30].

14.1.3.6 Pathology

The hallmark of pseudomonilethrix can be observed by light microscopy, as nodes 0.75–1 mm in length interrupt the hair at irregular intervals. Internodes are of normal hair shaft thickness. Using magnifications up to 3000× in electron microscopy, the "nodes" appear to be an optical illusion. Actually, the hair is indented at these regions, as the sides of the indentation protrude beyond the normal diameter of the shaft. Irregular twists of 25°–200° without flattening of the shaft can be observed. Essentially, scales are normal along the whole hair shaft (Fig. 14.4).

14.1.3.7 Differential Diagnosis

Monilethrix has to be differentiated by light microscopic examination, showing regular nodes and internodes in contrast to irregular nodes in pseudomonilethrix. In contrast to monilethrix, neither keratosis pilaris nor any other associated defects have yet been reported.

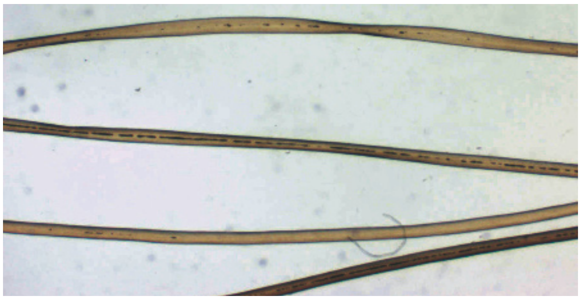


Fig. 14.4 Irregularly spaced nodes and internodes along the hair shaft in light microscopy are found in pseudomonilethrix

14.1.3.8 Treatment

The avoidance of trauma is the most effective method of managing this hair anomaly.

14.1.4 Pili Torti

Synonyms
pili torti OMIM 261900, pili torti and nerve deafness, Björnstad syndrome OMIM 262000, twisted hair, corkscrew hair

14.1.4.1 Introduction

Pili torti show a distinct hair shaft anomaly with increased fragility and can be classified into two groups: a classic early-onset Ronchese type and a late-onset Beare type. In addition, pili torti can be associated with copper deficiency (e.g., in Menkes disease) or with ectodermal defects and syndromes (e.g., Crandall's or Björnstad syndrome).

14.1.4.2 History

Pili torti were first discussed in the context of monilethrix by Schutz in 1900 [80]. Later on, Ronchese described congenital pili torti in detail [4].

14.1.4.3 Epidemiology

Pili torti may be congenital, sporadic or acquired. Congenital pili torti may be isolated or in association with other abnormalities and syndromes. *Classic pili torti* is

more common in females, primarily those with thin blond hair. The hair may be abnormal from birth or it may become abnormal in the early years of life. In early-onset pili torti, the pattern of inheritance is variable, and both autosomal-dominant and automsomal-recessive forms have been reported. The *late-onset Beare type* tends to manifest as patchy scalp alopecia after puberty. It presents as an autosomal-dominant condition [4]. Other defects have been reported in association with pili torti, as in Basex syndrome, Rapp-Hodgkin hypohidrotic ectodermal dysplasia, Menkes syndrome and familial acne conglobata. Pili torti have been sporadically found in other hair shaft anomalies such as monilethrix, pseudomonilethrix, woolly hair, longitudinal groves, trichorrhexis nodosa, and trichorrhexis invaginata.

14.1.4.4 Pathogenesis

Possibly, a fault in the inner root sheath impairs the molding of the growing hair shaft, leading to twisting of the hair. Taking into account that axillary and pubic hair are normally twisted and associated symptoms and defects are variable in pili torti, the underlying pathomechanism remains obscure.

14.1.4.5 Clinical Features

In *classic pili torti* (Ronchese) the hair is fragile, breaks easily and alopecia starts on the temporal and occipital areas, occasionally affecting eyebrows and lashes. *Late-onset Beare type* presents with spangled, dry, brittle hair that breaks at different lengths and may stand out from the scalp. The hair tends to be short, especially in areas subject to trauma. Classic pili torti may also be part of an ectodermal dysplasia syndrome, associated with keratosis pilaris, widely spaced teeth, nail dystrophy, corneal opacities, cleft lip palate, and occasionally ichthyosis. Other defects have been reported with pili torti: facial deformities, syndactyly of digits, mental retardation and also palagonia type of acrofacial dysostosis with oligodontia, normal intelligence, syndactyly, attenuation of 4th metacarpals, short stature, cleft lip, and vertebral anomalies [85]. In some pedigrees with late-onset type [9], mental retardation was present. In a number of patients sensorineural loss of hearing (cochlear type) has been reported in association (Björnstad syndrome). The latter emphasizes the importance of early auditory testing in children with this hair structure defect. Moreover, pili torti and sensorineural deafness are found together with hypogonadism in Crandall's syndrome. So-called corkscrew hair, a variant of pili torti, has been described in association with widely spaced teeth and syndactyly of fingers and toes. *Acquired pili torti* are mainly localized or patchy and are due to repetitive trauma. Pili torti are found in cicatricial alopecias of various origins, possibly due to distortion of the hair follicle caused by fibrosis.



Fig. 14.5 Light microscopy of pili torti showing a flattened hair shaft twisted through 180° on its longitudinal axis

14.1.4.6 Pathology

In light microscopy of pili torti, a flattened hair shaft twisted through 180° on its own longitudinal axis is found. Twists are found irregularly along the hair shaft. The phenomenon of many hairs twisted in a double spiral is called corkscrew hair (Fig. 14.5).

14.1.4.7 Differential Diagnosis

Isolated twisted hairs are also seen in normal scalps. In pili torti, these hairs are present at a remarkably high number and density. Monilethrix is often confused with pili torti, since irregular torsions along the hair shaft resemble the moniliform appearance. In addition, pili torti could indicate a carrier status for the Menkes disease gene. Moore and Howell [61] found pili torti in all affected males and in 43% of 28 obligate carriers or females at risk. Pili annulati should be differentiated in light microscopic analysis. Light and dark bands are seen along the hair shaft without twisting. This hair shaft anomaly does not cause increased fragility, but a distinct appearance of the hair with intermittent light and dark bands. Pili annulati, or ringed hair, may also be found in woolly hair. Children present with curled hair which is difficult to comb. In children with spun glass hair or uncombable hair, pili trianguli et canaliculi are found and may be confused with pili torti. Characteristic findings are triangular or kidney-shaped hairs seen in cross-sections and longitudinal grooves which are responsible for the frizzy, stand-away appearance of uncombable hair (Fig. 14.6a,b, Table 14.3).



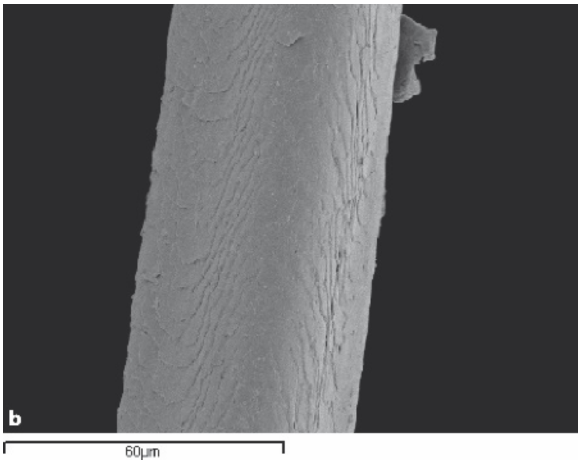


Fig. 14.6 **a** Typical frizzy and stand-away appearance of uncombable hair in a 6-year-old girl; **b** characteristic pili trianguli et canaliculi in scanning electron microscopy

14.1.4.8 Treatment

With regard to the hair shaft anomaly, the condition often improves over a number of years, particularly after puberty. There is no causative treatment of pili torti. Patients should be advised to minimize trauma to the fragile hair.

14.1.5 Menkes Disease

Synonyms
Menkes syndrome, kinky hair disease, Steely hair disease, copper transport disease OMIM 309400

14.1.5.1 Introduction

Menkes disease is a highly lethal, X-linked recessive disorder of copper metabolism dominated by neurodegenerative symptoms and connective tissue disturbances presenting hair with increased fragility due to pili torti.

14.1.5.2 History

Pili torti with copper deficiency was first described by Menkes [59] and colleagues in 1962. In 1988, Menkes listed six cuproenzymes, five of which may account for features of the disorder: tyrosinase for depigmentation of hair and skin pallor; lysyl oxidase for frayed and split arterial intima (defect in elastin and collagen cross-linking); monoamine oxidase for kinky hair; cytochrome c oxidase for hypothermia; and ascorbate oxidase for skeletal demineralization. Dopamine-beta-hydroxylase is also a cuproenzyme; what role its deficiency may have in the phenotype of kinky hair disease is unclear [59].

14.1.5.3 Epidemiology

In Menkes disease, an X-linked recessive disorder of copper metabolism, the incidence is estimated at about 1 patient per 254,000 live-born babies in Europe [94]. In Asia, the incidence of live-born patients has been reported to be 2.8 per million live births and 4.9 per million male live births [38].

14.1.5.4 Pathogenesis

Menkes disease is an infantile neurodegenerative disorder caused by mutations in ATP7A, an X-chromosomal gene that encodes a copper-transporting P-type ATPase. Recent findings support the localization of the Menkes locus (MNK) to Xq13, with a suggested fine mapping to sub-band Xq13.3 [98]. Deficiency of the ATP7A gene product results in abnormal cellular copper transport and reduced activities of numerous copper-dependent enzymes. Deficiency of lysyl oxidase, a copper enzyme involved in extracellular matrix metabolism via oxidation of lysine residues in elastin and collagen, may cause

generalized vascular tortuosity in patients with Menkes disease [35].

14.1.5.5 Clinical Features

Affected infants may develop normally until the onset of symptoms, usually between the age of 5 weeks and 5 months. Patients show characteristic white, steely, hair and neurological symptoms, such as seizures, delayed development, and muscular hypotony [13]. In Asians, hair color may also be brown or blond. Bony changes, resembling scurvy, tortuosities of the cerebral and systemic vasculature, and diverticuli of the bladder are also seen.

14.1.5.6 Pathology

In light microscopy, characteristic features of pili torti are found. The most diagnostic alteration is a marked reduction in blood copper and caeruloplasmin levels. Markedly decreased copper levels are also found in the brain and liver of affected boys.

Computed tomographic angiography is an accepted method for delineation of aneurysms, a possible feature in Menkes disease.

14.1.5.7 Differential Diagnosis

The recognition of Menkes disease may present problems in the early neonatal period. The serum copper and caeruloplasmin levels may be within the range of normal infants in the first week of life; they are higher than normal in the cord blood of affected infants and fall gradually after 4 weeks of age.

Pili torti may develop later, as the primary fetal hair is usually normal. The baby may appear bald, or both normal and abnormal hair may be found in different areas of the skull. The roentgenographic signs may not be evident until after 6 weeks of age. Menkes disease should be included in the differential diagnosis of unexplained rib and metaphyseal fractures, subdural hematomas, and neurological impairment in infants where the diagnosis of non-accidental injury such as that seen in the shaken baby syndrome is considered [63]. Other causes of epilepsy should be excluded. Bony changes resembling scurvy and vascular defects offer a broad spectrum of underlying diseases.

14.1.5.8 Treatment

The prognosis is poor and most of the patients die within the first 3 years of life. Various therapeutic attempts with parenteral administration of copper-histidine complexes have been made, with rather discouraging results. However, when copper-histidine complexes are supplied before manifestation of neurological or developmental defects, prognosis can be influenced to a certain extent [97]. Copper-histidine treatment bears the potential risk of copper overload and induced liver cirrhosis.

14.1.6 Netherton Syndrome

Synonyms
Netherton disease, Netherton syndrome, Netherton's syndrome, bamboo hair OMIM 256500

14.1.6.1 Introduction

The term "bamboo hair" refers to a distinctive hair shaft abnormality found in a rare syndrome, termed Netherton syndrome, which combines ichthyosiform skin changes, mainly consistent with ichthyosis linearis circumflexa Comèl and frequently an atopic state. In addition, erythroderma present at birth may also be found in association with the disease.

14.1.6.2 History

Ichthyosis linearis circumflexa was first described by Dr Comèl in 1949. It consists of migratory polycyclic erythematous patches surrounded by a serpiginous overlying double-edged scale. Patients report migration of erythema as much as 0.5 mm/day. In 1958, Dr EW Netherton described the bamboo-like deformity in the fragile hairs of a girl with erythematous scaly dermatitis. Netherton syndrome has evolved with observation of patients to include the triad of trichorrhexis invaginata, ichthyosis linearis circumflexa, and an atopic diathesis. Confusion has developed regarding patients who appear to have ichthyosis linearis circumflexa alone; however, trichorrhexis invaginata is a necessary finding in the diagnosis of Netherton syndrome [27].

14.1.6.3 Epidemiology

This rare disorder is inherited in an autosomal-recessive fashion. A dispute over gender predominance exists, with the thought that girls are much more commonly affected than boys, but Smith and co-workers showed 20 out of 44 cases to be male [88]. The incidence of Netherton syndrome is estimated to be 1 in 200,000. Netherton

syndrome is also thought to be the cause of up to 18% of congenital erythrodermas. The hair defect appears in infancy within the first 3 years of life and affects all hair to a certain degree [88].

14.1.6.4 Pathogenesis

Available evidence suggests that the defect is located on chromosome 5q32 [19]. Recently, SPINK5, which encodes the serine protease inhibitor Kazal-type 5 protein (LEKTI), has been identified as the defective gene in Netherton syndrome [10].

14.1.6.5 Clinical Features

Trichorrhexis invaginata causes patchy hair thinning, but sometimes complete alopecia. The remaining scalp hair has a dry, lusterless appearance. Eyelashes and eyebrows are sparse or absent. Ichthyosiform erythroderma may be present at birth or can develop within the first few weeks postpartum. A collodion membrane is rarely present at birth. Most children are affected with ichthyosis linearis circumflexa and generally show a normal development (Fig. 14.7). However, patients with erythrodermic Netherton syndrome often fail to thrive and suffer from hypernatraemia, hypothermia, recurrent infections, and septicemia, resulting in high postnatal mortality. The initial erythroderma usually evolves into ichthyosis linearis circumflexa over time. Patients also have features suggestive of atopic dermatitis with erythema and lichenification at flexural creases and diffuse generalized xerosis. In addition, mental deficiency, neurologic deficits (either seizure disorders or spastic diplegia), delayed growth and body development, short stature, recurrent infections (skin, eye, upper or lower respiratory tract), and hypogammaglobulinemia or hypergammaglobulinemia have been reported in affected individuals.



Fig. 14.7 Ichthyosis linearis circumflexa on the hand of a 7-year-old girl

14.1.6.6 Pathology

Findings in light microscopy compromise one or more nodes or nodular fractures, irregularly distributed along the affected shafts. The abnormal, tulip like invagination along the shaft is responsible for the extreme fragility of the hair, not allowing the hair to reach its normal length (Fig. 14.8a,b). In some cases, the pathological findings

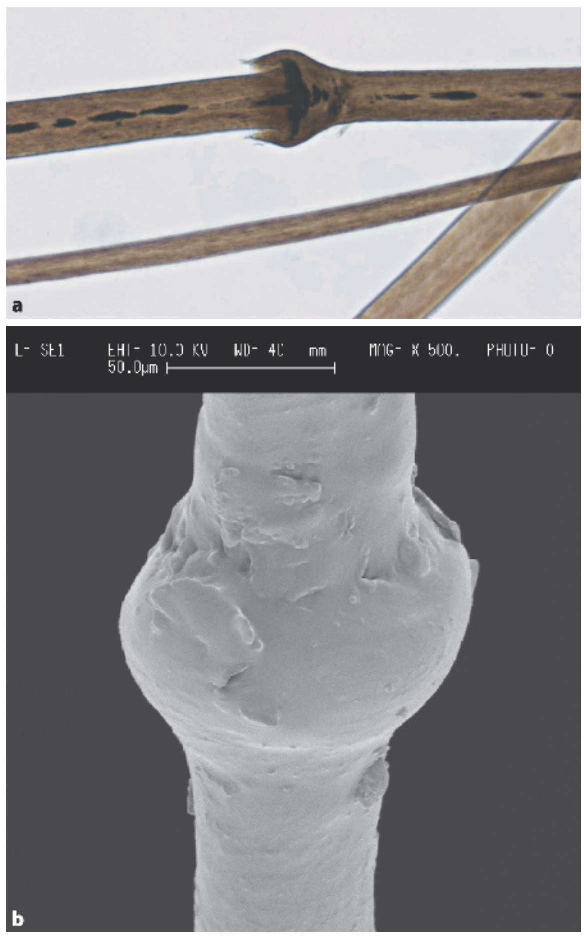


Fig. 14.8a,b In Netherton Syndrome a tulip-like invagination with "cup and ball" portion along the shaft demonstrated by (**a**) light microscopy and (**b**) scanning electron microscopy

are more prominent in vellus hairs than in terminal scalp hairs. Typical ultrastructural findings in histology are suppression of cornification characterized by the absence or massive reduction of keratohyalin granules, decrease of keratin filaments and premature exocytosis of lamellar bodies in the intercellular spaces of the stratum corneum.

14.1.6.7 Differential Diagnosis

Trichorrhexis invaginata is considered to be pathognomonic in Netherton syndrome, but may be difficult to detect in infancy and early childhood. Differential diagnoses include generalized seborrheic dermatitis, erythrodermic psoriasis, congenital non-bullous ichthyosiform erythroderma, and staphylococcal scalded skin syndrome (SSSS). Congenital ichthyosis, erythrodermic psoriasis or generalized seborrheic dermatitis can be excluded based on histology. In addition to its histological features in SSSS, bacteriological skin smears are negative.

14.1.6.8 Treatment

Patients with Netherton syndrome are likely to be more susceptible to systemic absorption of medication, and are therefore at increased risk of experiencing adverse reactions to topical therapies. Exfoliative erythroderma and hypernatremic dehydration with an increase of serum levels of urea after local treatment with an ointment containing 5% urea, 5% NaCl and 5% lactate four to five times daily has been reported. Case reports highlight significantly elevated serum tacrolimus levels in children with Netherton syndrome. Use of tacrolimus ointment in patients with Netherton syndrome should be reserved for the short-term management of flares on a limited body surface area and should be considered only when the benefits clearly outweigh the risks [82]. A crucial point in topical therapy is an intensive skin care of application of hydrophobic creams without additives or with a low dose of urea, for treating only specific parts of the body surface daily. Systemic administration of retinoids is discussed controversially in the literature, but might be beneficial when older and particularly in milder forms. The oral retinoid therapy may not heal the basic defect, but keratinization seems to normalize and hair can clinically improve. In addition, hair growth may improve with age [62].

14.1.7 Trichothiodystrophy

Synonyms

Ichthyosiform erythroderma with hair abnormality, mental and growth retardation, trichothiodystrophy with congenital ichthyosis, Tay syndrome, photosensitive trichothiodystrophy (TTDP), BIDS (Amish brittle hair brain syndrome, TTDN1), IBIDS or PIBIDS syndrome OMIM 601675

14.1.7.1 Introduction

Trichothiodystrophy (TTD) refers to a heterogeneous group of autosomal-recessive disorders that share the distinctive features of short, brittle hair and abnormally low sulfur content [73].

14.1.7.2 History

In two brothers and a sister, with first-cousin parents of Chinese extraction, Tay [93] described in 1971 a new autosomal-recessive disorder characterized by nonbullous ichthyosiform erythroderma, growth and mental retardation, somewhat progeria-like appearance, and short, sparse, lusterless hair that microscopically showed pili torti and trichorrhexis nodosa. Trichothiodystrophy (TTD) is a term introduced by Price and co-workers in 1980 [73] for sulfur-deficient brittle hair and associated symptoms.

14.1.7.3 Epidemiology

Within the spectrum of the TTD syndromes, numerous interrelated neuroectodermal disorders exist. Abnormalities in excision repair of ultraviolet- (UV-) damaged DNA are recognized in about half of the patients.

14.1.7.4 Pathogenesis

Three distinct autosomal-recessive syndromes are associated with nucleotide excision repair (NER) defects: the photosensitive form of TTD, xeroderma pigmentosum, and Cockayne syndrome. Genetically, three complementation groups have been characterized among photosensitive patients with TTD. Most patients exhibit mutations on the two alleles of the XPD gene. Mutated XPB gene or an unidentified TTD-A gene rarely results in TTD. In UV-sensitive TTD, the TFIIH transcription factor containing XPB and XPD helicase activities, nec-

essary for both transcription initiation and DNA repair, is damaged [46]. Recently, C7orf11 (TTDN1) was identified as the first disease gene for the non-photosensitive form of TTD, being mutated in two unrelated cases and in Amish kindred [16]. Hair of affected patients shows shaft abnormalities such as trichoschisis, trichorrhexis nodosa, or ribbon/twist, which is inversely correlated to the sulfur content of the hair. Raman spectra of hairs from TTD patients and normal donors show that there is a higher contribution of energetically less favored disulfide conformers in TTD hairs. These changes make TTD hairs excessively prone to breakage and weathering [54].

14.1.7.5 Clinical Features

Patients with TTD share the distinctive feature of short, brittle hair. The presence of low sulfur content in hairs and one of trichoschisis, tiger-tail pattern by polarizing light microscopy or severe cuticular damage by scanning electron microscopy are mandatory for diagnosing TTD. Persistent alopecia of the scalp is often found; eyebrows, eyelashes and body hair may also be affected. Associated clinical symptoms include physical and mental retardation of different severity, nail and dental dysplasias, cataracts, ichthyosis, premature aging, and, in half of the patients, photosensitivity. TTD syndromes include BIDS (brittle hair, intellectual impairment, decreased fertility, short stature), IBIDS (ichthyosis and BIDS), and PIBDS (photosensitivity and IBIDS).

14.1.7.6 Pathology

The hair has markedly low sulfur (cystine) content and presents characteristic light and polarizing features, the so-called tiger-tail pattern: alternating light and dark bands (Fig. 14.9). This characteristic pattern may be absent at birth and in the neonatal period. However, in biopsy samples of fetal eyebrows, lower cystine levels (19 µm/l) compared to age-matched control (368 µm/l) can be found at the second trimester [75]. In addition, trichorrhexis-nodosa-like fractures or trichoschisis may be found.

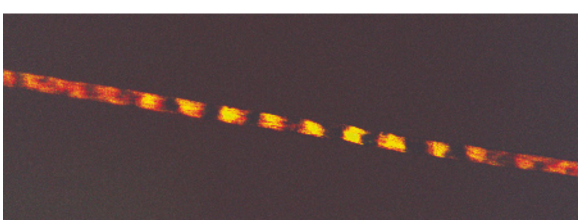


Fig. 14.9 Trichothiodystrophy shows characteristic features in polarizing light microscopy: the "tiger-tail" pattern with alternating light and dark bands along the hair shaft

14.1.7.7 Differential Diagnosis

Trichothiodystrophy has a broad spectrum of differential diagnoses since various clinical features are associated. Mainly, forms of erythrodermic ichthyosis, collodium baby and progeroid syndromes should be considered. Xeroderma pigmentosum, Cockayne syndrome and TTD share increased photosensitivity and display severe progeroid symptoms. Although caused by defects in genome maintenance via the nucleotide-excision, DNA-repair pathway, Cockayne syndrome and TTD patients appear to lack any cancer predisposition. In Cockayne syndrome, "cachectic dwarfism" describes the outward appearance of afflicted individuals. Other features include cutaneous photosensitivity, thin dry hair, a progeroid appearance, progressive pigmentary retinopathy, sensorineural loss of hearing, dental caries, and a characteristic "horse-riding" stance. Primarily, the distinct hair pathology presenting with tiger-tail pattern or trichoschisis together with its low sulfur content is the key to identifying TTD.

14.1.7.8 Treatment

In contrast to patients with xeroderma pigmentosum, no increase in skin cancer in patients with TTD has been observed. However, early prevention of sun-induced skin damage is necessary in photosensitive patients. Dietary cytosine supplementation has been suggested, but its value is unproven.

14.1.8 Ectodermal Dysplasia

Synonyms
OMIM NA

14.1.8.1 Introduction

Ectodermal dysplasias (EDs) represent a large and complex group of diseases comprising more than 170 different clinical conditions. Hair shaft anomalies are found in some cases, e.g., pili torti were reported in Crandall's or Björnstad's syndrome [23, 99]. In general, hair may be sparse, curly, and fair. Alopecia may be due to a hair

shaft anomaly with increased fragility, or to hypotrichosis. Hair shaft anomalies such as pili torti are not specific for a certain subgroup of ectodermal dysplasias. Eyebrows or eyelashes may be sparse, malformed or absent.

14.1.8.2 History

The ectodermal dysplasias are a heterogeneous group of conditions primarily affecting the hair, teeth, nails, and skin, and are classified according to the tissue(s) affected. Several classifications of EDs have been already proposed: Pinheiro and Freire-Maia [67] reviewed EDs from a clinical point of view; Priolo et al. [74] integrated both molecular genetic data and corresponding clinical findings. In the light of the recent discovery of causative genes for EDs, a classification according to their function has been proposed by Lamartine [51].

14.1.8.3 Epidemiology

Ectodermal dysplasias are rare diseases with an estimated incidence of 7 out of 10,000 births for all EDs [58]. Of the 170 EDs described so far, fewer than 30 have been explained at the molecular level with identification of the causative gene [51].

14.1.8.4 Pathogenesis

Ectodermal dysplasias feature impaired development of ectodermal appendages. Their development is regulated by a sequence of inductive interactions between two adjacent tissue layers, the epithelium and the mesenchyme. Recent evidence implicates a genetic defect in different pathways, which orchestrate ectodermal organogenesis. Embryogenesis is regulated by a number of complex signaling cascades that are critical for normal development. One of the best investigated pathways is the sonic hedgehog, leading to interactions with the transcription factors within the Gli family. Dysregulation of the sonic hedgehog-patched gli pathway may lead to different diseases including some from the spectrum of EDs [74].

14.1.8.5 Clinical Features

Often, alopecia is a feature of subtypes in ectodermal dysplasias. Hair is generally fair and scanty, sometimes brittle and uncombable. Body hair is often diminished or absent. Eyebrows and eyelashes may be lacking. In general the skin is dry and fine.

From a clinical point of view, two main groups, specified as A and B, are helpful in looking for morphologic features in the child (Table 14.4, [45]). All entities having defects in at least two of the classical ectodermal structures such as hair, teeth, nails, and sweat glands belong to group A. Group B only has defects in one of the four above-mentioned structures, plus one other ectodermal defect, such as anomaly of ears, lips, or dermatoglyphics

Table 14.4 Clinical manifestations in ectodermal dysplasias. Group A: defects in at least two of the following ectodermal structures: hair, teeth, nails and sweat glands. Group B: defects in only one of the ectodermal structures hair, teeth, nail and sweat glands plus one other ectodermal defect, e.g., ears, lips, dermatoglyphics on palms and soles [45]

Abnormalities in hair follicles
Sparse, curly, and fair hair
Alopecia because of hypotrichosis or increased hair fragility
Eyebrows or eyelashes absent/sparse or malformed
Dental changes
Hypodontia or anodontia
Malformed teeth with cone- or peg-shaped aspects
Prone to caries because of enamel defect or salivary gland malfunction with xerostomia
Nail changes
Leukonychia
Dystrophic and malformed nails
Impaired sweat gland function
Absence, reduction or increase of sweating
Hyperthermia under warm conditions
Skin alteration
Superficial dry scaling skin at birth
Dry and often hypopigmented skin
Dermatitis resembling atopic skin disease
Eye abnormalities
Corneal dysplasias
Cataract
Displaced or stenotic lacrimal puncta
Defective or decreased lacrimation



Fig. 14.10 Ectodermal dysplasia type B. Abnormal shaped teeth



Fig. 14.11 Ectodermal dysplasia type B. Hyperkeratosis of the palms and soles, and bone anomalies (pes equinovarus, not shown)

on palms and soles (Figs. 14.10, 14.11). A disease which features only ectodermal signs is named a pure ectodermal dysplasia. A combination with other anomalies is named ectodermal dysplasia syndrome [45, 67].

The molecular classification of known genes causative of EDs and of their related diseases allows a genotype–phenotype correlation of these disorders. Another classification of EDs defines groups that are homogeneous and comparable from a clinical point of view, with respect to the molecular classification of causative genes. Several interactions among genes from different groups (especially groups II and IV) along common pathways of action have been noted [74]. Group I is composed of the so-called pure EDs, in which only epidermal derivative abnormalities are present. Identified causative genes are EDA1 and DL. Group II includes diseases characterized by premature aging. Identified causative genes are ERCC2, ERCC3 and RECQL4. Group III constitutes multiple congenital anomalies/EDs in which skeletal abnormalities are always present. Identified causative genes are p63, DLX3, TRPS1, and EVC. Group IV includes syndromic EDs characterized by premature aging and predisposition to neoplasias. The identified causative gene is DKC1. Group V diseases are all characterized by skin-associated disorders, such as keratoderma and skin fragility. Identified causative genes are KRT 16, KRT 6a, KRT 17, KRT 6b, PKP1, LOR, and CTSC. Members of the RecQ family (group II) are likely to be involved in normal telomere maintenance and cell aging. Dkc protein (group IV) is also involved in the same mechanisms. Accordingly, dyskeratosis congenita has several clinical features in common with Rothmund-Thomson syndrome, such as premature aging and predisposition to neoplasias. Based on these observations, it is clear that RECQ genes and DKC1 may interact in common pathways, thus explaining common clinical and biological features. Four additional groups classifying the remaining diseases with different clinical features are: Group VI, with deafness as major clinical criteria; Group VII, with ocular anomalies/retinal dystrophy; Group VIII, with renal abnormalities; and Group IX, with associated endocrine–neuroendocrine abnormalities [74].

14.1.8.6 Pathology

Thorough clinical examination is mandatory to identify the underlying ED. Caused by impaired development of epidermal appendages, EDs are characterized by a primary defect in at least one of the following tissues: nails (dystrophic, hypertrophic, abnormally keratinized), hair (hypotrichosis, partial or total alopecia), teeth (abnormal or absent), and sweat glands (hypoplastic or aplastic). In some cases pili torti are found. They follow all possible Mendelian modes of inheritance (autosomal-dominant or autosomal-recessive, X-linked dominant or recessive) but sporadic cases are also described.

14.1.8.7 Differential Diagnosis

A broad differential diagnosis is reflected by the different pathological conditions and clinical manifestations of EDs. In general, congenital hypotrichias and atrichias without other ectodermal defects should be considered.

14.1.8.8 Treatment

The prognosis and treatment depend on underlying defects, which are as heterogeneous as the group of EDs itself.

14.1.9 Acquired Hair Shaft Defects with Fractures: Weathering

Synonyms
cuticular weathering OMIM NA

14.1.9.1 Introduction

The term weathering is reserved primarily for all types of cosmetic manipulation, resulting in defects of the hair shaft. Hair consists of highly organized and orientated keratinized fibers and fibrils; and these can be modified by cosmetic procedures to give a variety of styles.

14.1.9.2 History

All through the ages, cosmetic procedures to change or enhance the outer appearance have been utilized. Hair in particular is a main target of modification, regarding quality, quantity, structure, and color.

14.1.9.3 Epidemiology

Depending on cultural aspects, hair styles differ worldwide in every country and population. However, repeated physical or chemical trauma of the hair shaft due to styling procedures may lead to hair defects with increased fragility.

14.1.9.4 Pathogenesis

In weathering, the damage to cuticular cells subsequently leads to loss of their cortex-protecting capacities and to breakage. In bubble hair, a reproducible cause has been established. Brief, focal heating of damp hair is sufficient to cause bubbles to form inside the hair fibers. This in turn results in weak, dry and brittle hair, which easily breaks.

The most common cause of acquired hair fracture is trichorrhexis nodosa due to physical or chemical trauma. A contributory factor is an inherent weakness of the hair shaft. In the proximal type, some authors consider the excessive structural damage observed in African hair shafts is consistent with physical trauma (resulting from grooming) rather than an inherent weakness due to any structural abnormality. In contrast to the distal type, in the circumscribed type, a clear history of an underlying trauma is not always found. Frequent twisting and manipulation of the beard may be sufficient to break the twisted fibers of the beard and moustache as seen in chronic rubbing of these areas. In general, fractures of the hair shaft present as trichoschisis, trichoclasis or trichoptilosis.

14.1.9.5 Clinical Features

Bubble hair is characterized by weak, dry and brittle hair that breaks easily. Acquired trichorrhexis nodosa is found in the proximal or in the distal part of the hair shaft or maybe localized, as in patches of trichotillomania, lichen simplex chronicus or pruritic dermatoses [104]. *Proximal trichorrhexis nodosa* is mainly found in patients who are invariably Afro-American with a family history of short hair, but the genetic background is still under discussion. *Distal trichorrhexis nodosa* is seen primarily in Caucasians and Asians of both sexes. Both forms are acquired due to repeated trauma contributing to cuticular damage [14, 48]. *Circumscribed trichorrhexis nodosa* occasionally occurs in the scalp hair, moustache or beard, as a small patch.

14.1.9.6 Pathology

Bubble hair is characterized by bubble-like areas in the hair shaft seen with light microscopy and corresponding cavitary defects with scanning electron microscopy. Electron microscopy reveals a loss of cortical cells and medulla. Cross-section images showed either a single large cavity or a reticulated, "Swiss cheese-like" loss of cells. In trichorrhexis nodosa, hair mount shows broken segments of hairs and typical trichorrhexis nodosa fractures along the hair. Trichoschisis is a clean, transverse fissure or fracture through the hair shaft and localized absence of cuticle cells. A classic greenstick fracture is called trichoclasis, showing a shaft splinted in part by an intact cuticle. Longitudinal splitting of the hair shaft at its distal end leads to the common split ends, called frizzies or trichoptilosis (Fig. 14.12).

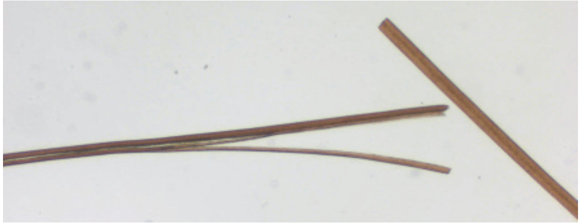


Fig. 14.12 In trichoptilosis, longitudinal splitting is found at the distal end of the hair shaft

14.1.9.7 Differential Diagnosis

In weathering, typical hair splitting at the hair tip or the upper hair is found. Depending on the cosmetic procedure not all hairs are affected, e.g., underlying hairs close to the scalp sometimes are less or not affected. In hair mount and light microscopy, pili torti, bamboo hair or monilethrix should be differentiated from trichorrhexis nodosa. Longitudinal embedding of hair shafts is helpful to identify the distinct hair shaft morphology in these hair defects. Bubble hair does not show a regular pattern like the tiger tile pattern in trichothiodystrophy using polarizing light. However, trichoschisis, trichoclasis or trichoptilosis is easily identified.

14.1.9.8 Treatment

In weathering, children and their parents should be advised to cease all chemical or physical hair manipulation. A wide-toothed, round-tipped comb or a soft brush is recommended. Hair conditioners are helpful and a cream rinse applied to the hair ends after shampooing minimizes tangling of the hair. Affected ends should be cut and hot hair dryers should be avoided completely.

14.2 Localized Hair Loss

Localized hair loss in children mainly presents as various degrees of non-scarring alopecia. However, in any type of localized hair loss a close inspection of the skin should be performed to differentiate between non-scarring or scarring alopecia. Inspection with dermoscopy of the scalp in affected areas is a non-invasive and easy tool to characterize the type of alopecia and detect early signs of scarring [78].

14.2.1 Non-Scarring Alopecia

14.2.1.1 Alopecia Areata

Synonyms
pelade, alopecia universalis OMIM 104000

14.2.1.1.1 Introduction

Alopecia areata is a chronic inflammatory disease characterized by patchy, non- scarring hair loss with T-cell infiltration of hair follicles.

14.2.1.1.2 History

The first citation of alopecia areata is estimated about several decades Anno Domini. Later in 1706, Sauvages used the term “alopecia areata” in his *Nosolgia Medica*. Despite parasitic hypothesis in the nineteenth century, the autoimmune pathogenesis in genetically susceptible patients was established in the twentieth century [44].

14.2.1.1.3 Epidemiology

Alopecia areata is a common cause of non-scarring hair loss in children mostly older than 3 years. In newborns and very young infants, however, it is thought to be rare [24]. It occurs in approximately 0.1% of the general population [79], but in approximately 9% of patients with Down syndrome [18].

14.2.1.1.4 Pathogenesis

Substantial evidence indicates that genetic factors may have a role in the etiology of alopecia areata. In general, there is evidence of genetic heterogeneity in alopecia areata and its different clinical pattern [32, 100]. C3H/HeJ mice spontaneously develop alopecia areata. Recent evidence suggests a major locus on mouse chromosome 17 and minor locus on chromosome 9 linked with alopecia areata in C3H/HeJ mice [90]. Fas-deficient C3.MRL-Tnfrsf6(lpr) mice do not develop hair loss, suggesting that the Fas pathway plays a pathogenetic role in alopecia areata [31]. However, the exact locus has not been identified (see Chap. 15).

14.2.1.1.5 Clinical Features

Different degrees of non-scarring alopecia are found in patients with alopecia areata: round or oval patches (alopecia areata circumscripta, Fig. 14.13), complete alopecia of the scalp (alopecia areata totalis) or of the scalp and body hair (alopecia areata universalis), band-like alopecia on the occiput (ophiasis-type), and rarely diffuse alopecia (diffuse-type).

Atopic state (approx. 40%) and thyroid diseases (approx. 29%) are frequently found. Alopecia areata has also been associated with other autoimmune diseases, e.g., vitiligo, lupus erythematosus, rheumatoid arthritis, pernicious anemia, scleroderma, inflammatory bowel disease, myasthenia gravis, and lichen planus.



Fig. 14.13 Non-scarring alopecic patches in a 5-year-old boy with patchy alopecia areata

14.2.1.1.6 Pathology

The pull-test may be performed to evaluate the activity of the disease. In selective and unclear cases, a trichogram may help to exclude other causes of localized non-scarring hair loss. In acute cases, elevated rates of telogen and dystrophic hairs are found at the margin of the lesions. In difficult cases, histological evaluation may be performed showing a typical T-cell infiltrate, like a "swarm of bees," around the bulb region.

14.2.1.1.7 Differential Diagnosis

If the onset of complete alopecia is in infancy one should consider alopecia with papular lesions (APL) as the differential diagnosis. At birth, the hair usually appears normal on the scalp, but alopecia develops shortly after birth. A scalp biopsy shows few hair follicles, dilated and without hairs, and the absence of an inflammatory infiltrate. In patchy-type alopecia areata, other forms of localized, non-scarring alopecia should be taken into account. Most common is tinea capitis, showing scaling, sometimes erythema and pustules at the border of the lesion. Also, trichotillomania may be confused with alopecia areata. Trichogram reveals predominantly anagen hairs and nearly absent telogen hairs, in contrast to increased telogen and dystrophic hairs in alopecia areata. In addition, triangular alopecia could be confused with patchy alopecia areata. Early stage of linear morphea can present as a single alopecic patch with very decent brownish macula without clinical evidence of scarring. If suspected, it should be excluded by histology.

14.2.1.1.8 Treatment

According to clinical pattern, a poor prognosis may be estimated if alopecia areata occurs before puberty, a positive family history is given, more prolonged (> 2 years) and extended forms of the disease are present (alopecia areata totalis or universalis and ophiasis-type), there is nail involvement, and if associated autoimmune disorders are found. Depending on estimated prognosis and age the individual therapeutic concept should be established. For further details please see Chap. 15 on alopecia areata.

14.2.1.2 Tinea Capitis

Synonyms
trichophytosis superficialis capillitii, trichophytia profunda capillitii, kerion celsi, favus, dermatomycosis, OMIM NA

14.2.1.2.1 Introduction

Tinea capitis is a dermatophytic fungal infection of the scalp that is particularly contagious among children.

14.2.1.2.2 History

In 1841, Gruby reported the infectious etiology of tinea capitis; he cultured both the infectious agent causing favus and reproduced the condition by inoculation into a human subject [77].

14.2.1.2.3 Epidemiology

Tinea capitis, a dermatophyte infection involving the hair shaft on the scalp, is primarily a disease of preadolescent children. The predominant pathogen varies according to the geographical location. *Microsporum* (*M.*) *canis*, *Trichophyton* (*T.*) *tonsurans* and *T. audunii* account for the majority of infections in certain parts of Europe and North America. Tinea capitis caused by *M.*

canis is a common mycosis of the scalp in children aged 1–3 years and 4–11 years [28].

14.2.1.2.4 Pathogenesis

Common sources of infection by *M. canis* are cats, if they have had contact with infected cats in Southern European countries and guinea pigs. The pathogens colonize in the fur of the animals, often without causing apparent clinical symptoms. Transmission by indirect contact, i.e., with objects (car seats, stuffed animals, etc.) as well as person-to-person contact has also been reported. Hair invasion can occur as an ectothrix or endothrix infection. In ectothrix infections, the fungus, predominantly arthroconidia (spores), attaches to the surface of the hair shaft. In endothrix infections, the pathogen invades the hair shaft without destroying the cuticle. Typical pathogens involved in ectothrix infection are *M. canis* and *M. audouinii* as well as *T. mentagrophytes* var. *granulosum*. Endothrix infection can be caused by pathogens such as *T. tonsurans* or *T. violaceum* [81].

14.2.1.2.5 Clinical Features

The clinical presentations are variable and include: (1) a "seborrheic" form that is scaling, often without noticeable hair loss; (2) a pustular, crusted pattern, either localized or more diffuse; (3) a "black dot" variety characterized by small black dots within areas of alopecia; (4) a kerion, which is an inflammatory mass [15]; and (5) a scaly, annular patch (Fig. 14.14). Favus is a specific type of tinea capitis characterized by scutula, which are sulfuric-yellow concretions of hyphae and skin debris at the orifices of hair follicles.

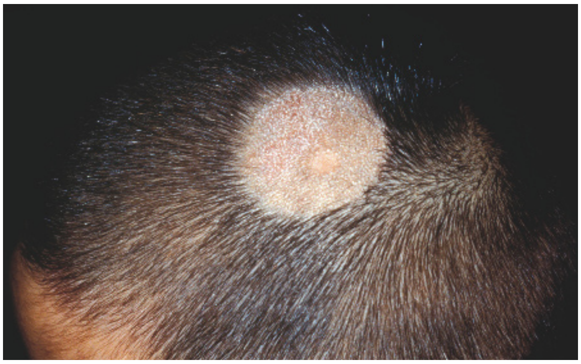


Fig. 14.14 Non-scarring alopecic patch in a 3-year-old boy covered with white, fine scales. Tinea capitis was diagnosed by fungal culture revealing *Microsporum canis* infection

14.2.1.2.6 Pathology

Tinea capitis is diagnosed both clinically and using culture [68]. Clinical diagnosis of tinea capitis is confirmed by unstained specimens and fungal culture. The lesion is disinfected with 70% alcohol and any crusts are carefully removed using tweezers. Hair or hair stumps are plucked from the margin around the lesion. Examination using a Wood light (UV lamp, 365 nm UVA rays) can be useful for diagnosis, particularly with epidemic infections. Yellowish-green fluorescence confirms a diagnosis of *Microsporum* infection (e.g., *M. canis*). It should be noted that Wood light examination does not offer a particularly high degree of sensitivity for diagnosing *M. canis* infection of the scalp and, thus, is not a suitable means of excluding infection.

14.2.1.2.7 Differential Diagnosis

Differentials include: psoriasis capitis, chronic contact eczema, atopic eczema, seborrhea capitis (after puberty), tinea amiantacea, alopecia areata, pyodermia, carbuncles, and occasionally, trichotillomania. However, cutaneous lupus erythematous and follicular lichen ruber are very rare in children.

14.2.1.2.8 Treatment

Although the oral antifungal agents are the most important aspect of therapy, adjunctive topical therapy is beneficial. Sporicidal shampoos can aid in removing adherent scales and hasten the eradication of viable spores from the scalp in the hope of decreasing the spread of this infection. Mainly, alopecia is non-scarring and hair regrows after sufficient treatment. In rare cases of deep fungal infection a scarring alopecia may remain. Thus, early diagnosis and efficient treatment is important in tinea capitis. (For further details see also Chap. 19).

14.2.1.3 Trichotillomania

Synonyms
OMIM NA

14.2.1.3.1 Introduction

Trichotillomania (TTM) is an impulse disorder, in which patients chronically pull hair from the scalp and/or other sites complaining of lack of hair growth or of hair loss.

14.2.1.3.2 History

Trichotillomania derives from the Greek; trich (hair), tillo (pull) and mania (excessive excitement), as described by Hallopeau [77].

14.2.1.3.3 Epidemiology

Very early onset of hair pulling in children under the age of 6 may be more benign and self-limiting than the more common syndrome of late-childhood-onset hair pulling. While far more women and adolescent girls appear for treatment, survey studies suggest that chronic hair pulling also occurs in males.

14.2.1.3.4 Pathogenesis

Trichotilomania is found in patients who have an irresistible compulsion to pull out or twist and break off their hair. Patients often exhibit complex behavioral patterns as part of an obsessive-compulsive disorder or an impulse control disorder. Telogen hairs are plucked out with ease; anagen hairs may be plucked or twisted and broken off at various lengths.

14.2.1.3.5 Clinical Features

Single or multiple nearly alopecic areas are found predominantly in the parietal and vertex regions (Fig. 14.15). Eyebrows, eye lashes, pubic hair, beard, and body hairs are rarely affected. Sometimes these areas show a bizarre or geometric pattern. Close clinical inspection may reveal petechiae on the scalp close to follicle infundibulum or dark spots in the infundibulum. A number of hairs always remain in this area. In addition, onychophagia (nail-biting) may be associated.



Fig. 14.15 An 11-year-old girl presented with a localized, non-scarring alopecia for >15 months. Trichotillomania was diagnosed after thorough clinical and psychological exploration and investigation. Psychological work-up succeeded in complete regrowth

14.2.1.3.6 Pathology

Trichogram examination shows nearly 100% of anagen hairs and missing telogen hairs. In addition, broken hairs with blunted or frayed ends are seen. Biopsy specimen may reveal hair cast remnants at about 60%. Also, suggestive for diagnosis is a predominance of catagen hairs, since plucking induces a shift from anagen to catagen. Traumatized hair follicles may show trichomalacia and perifollicular hemorrhages.

14.2.1.3.7 Differential Diagnosis

This entity can mimic the clinical appearance of many other forms of hair loss including alopecia areata, androgenetic alopecia, and tinea capitis. It is important to differentiate TTM from other forms of alopecia, because its treatment is quite different. Lack of telogen hairs showing nearly 100% of anagen hairs in the trichogram taken from the margin of the lesion is usually sufficient for differentiation. In rare cases, patients cut the hair leaving an area with short hair at a different length. This manipulation is called trichotemnomania, revealing a normal trichogram and clearly cut hairs in longitudinal embedded hairs.

14.2.1.3.8 Treatment

Specialized age-adapted psychotherapy, such as habit reversal training, is recommended; however, the treatment is intensive and highly specialized [102].

14.2.1.4 Traction Alopecia

Synonyms
traumatic alopecia, pony tail alopecia, OMIM NA

14.2.1.4.1 Introduction

Traction alopecia is traumatic hair loss secondary to the application of tensile forces to scalp hair.

14.2.1.4.2 History

Traction alopecia resulting from mechanical forces to hair has been in existence since the implementation of traditional methods of hair styling, but, to our knowledge, was first described in 1958 by Slepyan [86].

14.2.1.4.3 Epidemiology

Traction alopecia is quite common in black children, especially with curly hair, due to traditional methods of hair styling [52]. Transient neonatal shedding and occipital alopecia is quite common in newborns within the first weeks of life.

14.2.1.4.4 Pathogenesis

So far, the etiology of neonatal occipital alopecia has been reported to be friction. Recently, physiological shedding of hair in the first weeks of life has been identified as the cause of this phenomenon [25]. The pillow, which is often blamed, aids this shedding. Chronic traction of the hair may lead to transient alopecia. However, if continued over a period of time, permanent alopecia may develop due to atrophy of hair follicles.

14.2.1.4.5 Clinical Features

This condition can be classified as marginal or non-marginal. In neonates, circumscribed occipital hair loss is often found within the first weeks of life. Postnatal shedding and friction or pressure over the bony occipital prominence may contribute to this reversible phenomenon. In young girls, it may possibly be observed as “ponytail” alopecia, although traction may lead to loss of hair on any site of the scalp depending on the hairdressing techniques used. The clinical pattern of marginal alopecia or hypotrichosis in areas of chronic traction or friction frequently comprises mild perifollicular erythema. In some cases, chemical treatment of hairs in combination with friction leads to acute breakage of hairs, e.g., after use of agents to straighten hairs and combing of hair to a pony tail.

14.2.1.4.6 Pathology

The diagnosis of traction alopecia is generally performed clinically. To exclude other underlying diseases, a trichogram or TrichoScan is helpful and should present relatively normal values in traction alopecia. In chronic traction alopecia, a reduced numbers of hair follicles, sometimes with fibrous tracts, may be seen in scalp biopsy samples.

14.2.1.4.7 Differential Diagnosis

In neonates, non-marginal occipital alopecia may also be due to physiological hair shedding occurring 8–12 weeks postnatally. Different patterns of transient neonatal hair loss have been identified [25]. Marginal, often band-like, alopecia of the fronto-temporal region of the scalp may be confused with alopecia areata. In the latter case, the pull-test is positive. After traumatic injury to the scalp resulting in deep wounds, a cicatricial alopecia may result. Traumatic scarring lesions may occur due to accidents, burns, radiation or may be chemically induced [36, 105]. In loose anagen hair, large patches of alopecia may accidentally occur after pulling hairs. Hairs are easily pulled out without any pain and a trichogram shows nearly 100% anagen hairs.

14.2.1.4.8 Treatment

In either case, the induced trauma, often the result of cultural, social, and cosmetic practices, is unintentional. Initially, hair loss is reversible if trauma is discontinued; however, permanent alopecia may result from chronic traction [40]. For large scarring defects, surgical intervention may be required [103].

14.2.1.5 Triangular Alopecia

Synonyms
congenital triangular alopecia, brauer nevus OMIM NA

14.2.1.5.1 Introduction

Congenital triangular alopecia is manifested at 2–5 years of age by unilateral or, less frequently, bilateral patches of alopecia in the fronto-temporal region. Triangular alopecia is rarely present at birth or develops in adulthood.

14.2.1.5.2 History

About 52 cases of congenital triangular alopecia have been reported so far.

14.2.1.5.3 Epidemiology

Probably because the lesion is benign and non-progressive, an analysis in 6200 patients revealed 7 with triangular alopecia, a frequency of 0.11% [34]. Congenital triangular alopecia usually occurs sporadically but may exceptionally affect several members of a family [41].

14.2.1.5.4 Pathogenesis

The genetic basis of congenital triangular alopecia is not yet clear. It has been reported in association with phacomatosis pigmentovascularis, providing evidence that it may originate from loss of heterozygosity. Heterozygous individuals could be phenotypically normal. It may be a paradominant trait [41].

14.2.1.5.5 Clinical Features

In the triangular region of frontal scalp, a localized alopecia is found. The lesion is usually unilateral but bilateral involvement may likewise occur (Fig. 14.16).

14.2.1.5.6 Pathology

The alopecic area contains a normal numbers of hairs, although virtually all are vellus or indeterminate follicles.



Fig. 14.16 Triangular alopecia (Brauer nevus) was found as a unilateral non-scarring alopecic patch in a 14-year-old boy

14.2.1.5.7 Differential Diagnosis

The distinct clinical appearance characterizes the disease and helps to differentiate from androgenetic alopecia and alopecia areata.

14.2.1.5.8 Treatment

In general, the real need of treatment should be discussed with parents and patients. However, surgical treatment reducing the alopecia area is possible.

14.2.2 Scarring Alopecia

Localized scarring of the scalp in children is mainly found as aplasia cutis congenita. In addition, a severe physical, chemical trauma or a deep , fungal or viral infection of the scalp may result in a scarring alopecia after healing of the defect or infection.

14.2.2.1 Congenital Aplasia Cutis

Synonyms
aplasia cutis congenita, congenital defect of skull and scalp, congenital scalp defect, ACC, epitheliogenesis imperfecta OMIM 107600

14.2.2.1.1 Introduction

Aplasia cutis congenita is a congenital condition in which skin, bone, and dura can be absent. In the majority of cases, the scalp is affected, limited to the dermis and epidermis.

14.2.2.1.2 History

Aplasia cutis congenita was first described by Cordon in 1767 and more than 500 cases have been reported since [11].

14.2.2.1.3 Epidemiology

Aplasia cutis congenita is a rare condition with an estimated incidence of 2–3 cases per 10,000 newborns; 86% of all solitary lesions involve the scalp, although other parts of the body may be affected. Defects may involve the epidermis and dermis to varying degrees, and ap-

proximately 15% of the scalp defects also involve the underlying skull.

14.2.2.1.4 Pathogenesis

Aplasia cutis congenita is typically sporadic. However, autosomal-dominant and rarely autosomal-recessive cases have been reported. The exact pathophysiology underlying aplasia cutis congenita is unknown; however, several factors have been implicated. These include intrauterine trauma, vascular compromise, teratogens such as infectious agents, and methimazole, an antithyroid medication. However, a hypothesis of disruptive mechanical forces of tension and stretching on embryonic skin and its underlying mesenchyme has been supposed. An animal model of aplasia cutis congenita may exist in transgenic mice over expressing the glucocorticoid receptor. These mice are born with generalized thin skin, decreased hair growth, and localized absence of skin at the cranium and umbilical regions [11].

14.2.2.1.5 Clinical Features

Aplasia cutis congenita is a rare condition characterized by congenital absence of the epidermis, dermis, and subcutaneous tissue. It may occur as an isolated defect or associated with other anomalies. Vertex aplasia cutis typically ranges in size from 0.5 to 3 cm. The condition can present in isolation or with associated conditions such as limb anomalies or embryologic malformations (Fig. 14.17).



Fig. 14.17 Large defect with scarring alopecia in aplasia cutis congenita in a 2-day-old male term newborn. Magnetic resonance imaging revealed an underlying bone defect of the skull

14.2.2.1.6 Pathology

Careful study due to the frequent association of aplasia cutis congenita with other congenital anomalies and a complete obstetric and family history of all affected individuals are required to identify possible specific teratogens, intrauterine infections, chromosomal abnormalities, or history of this condition among relatives. Ultrasound and magnetic resonance imaging are important diagnostic tools to determine the extension of the lesion.

14.2.2.1.7 Differential Diagnosis

Diagnosis is made by characteristic clinical picture. However, small lesion with scarring alopecia at birth may not be noted. If discovered in older children, localized morphea should be excluded by skin biopsy in difficult cases.

14.2.2.1.8 Treatment

In small defects, secondary wound healing will result in permanent scarring alopecia. A conservative approach consisting of daily antiseptic dressing may allow scalp epithelialization to improve conditions for secondary surgery. The rare larger scalp defects are prone to complications of hemorrhage and infection. For large defects, surgical intervention is required [11].

14.3 Diffuse Hair Loss

Diffuse hair loss is a symptom representing a broad spectrum of underlying diseases. Mainly, different types of non-scarring alopecia should be considered. However, some forms of scarring alopecia may appear as a diffuse type of hair loss.

14.3.1 Non-Scarring Alopecia

In most cases of children presenting with diffuse hair loss, a telogen effluvium is diagnosed. The diffuse type of alopecia areata is rare, but this entity should be considered in differential diagnosis. Loose anagen hair is often found when parents complain of slowly growing hair. On the basis of numerous hair diseases and syndromes with congenital hypotrichosis or atrichia, this chapter may not include and discuss all known forms (see also Chap. 6 and review papers [2, 106]).

14.3.1.1 Telogen Effluvium

Synonyms
telogen hair loss, telogen hair shedding OMIM NA

14.3.1.1.1 Introduction

Generalized hair loss presenting as telogen effluvium is due to a parallel interruption of the anagen phase. Underlying causes are numerous and a careful diagnostic work up is mandatory to unravel the disorder.

14.3.1.1.2 History

Due to the variety of underlying causes, it is difficult to define a distinct history of first description of telogen effluvium. Since underlying disorders such as iron deficiency or thyroid dysfunction exist over a long period, one may assume that diffuse hair loss is apparent, because the underlying diseases have been identified.

14.3.1.1.3 Epidemiology

Telogen effluvium is a common cause of diffuse hair loss in children. Rarely is dystrophic effluvium diagnosed. The underlying cause varies but as iron deficiency and thyroid dysfunction are not uncommon in children, these disorders should be considered in telogen effluvium. Also, diffuse hair loss in children may occur after severe bacterial or viral infections.

14.3.1.1.4 Pathogenesis

Telogen effluvium is caused by the abrupt synchronous induction of growing hairs (anagen) into telogen phase. If an acute interruption of anagen by a highly toxic event occurs, anagen-dystrophic hairs may result instead of telogen hairs. This process can be triggered by a wide variety of systemic metabolic disorders and drugs. However, drugs are rather rarely the cause of telogen effluvium in children in contrast to adults. In chemotherapy hair loss is also noted, similar to adults.

14.3.1.1.5 Clinical Features

Children usually present with a history of abrupt generalized diffuse hair shedding and thinning over the entire scalp. In telogen effluvium the underlying cause may precede the onset of hair loss by about 3 months or less. Clinically, hair volume may be normal or diminished. A hair pull-test is positive throughout the scalp; usually 6–20 pulled hairs are painlessly extracted, provided the child's hair has not been shampooed for 48 hours.

14.3.1.1.6 Pathology

Pathological induction of telogen in children can often be due to iron deficiency, thyroid dysfunction, and after systemic infections with fever. Less often, underlying causes such as nutritional disorders, malabsorption, renal or hepatic failure and surgery are responsible. Common causative drugs in children include anticonvulsants, anticoagulants and antidepressants; rarely, hormones, retinoids, beta-blockers, angiotensin-converting enzyme inhibitors, and cholesterol-lowering agents are the cause. In case of predominantly dystrophic hairs, a severe underlying cause such as an acute metabolic disorder or failure should be considered; causative drugs are mainly chemotherapeutics.

A helpful, but for children painful, diagnostic tool is the trichogram technique. After pulling 50 hairs from the frontal and occipital regions, hairs are embedded in hair mount and analyzed under the microscope. More than 15% telogen hairs in both areas is indicative of diffuse telogen hair loss. An increased number of dystrophic hairs (> 3%) could be due to a severe underlying cause.

14.3.1.1.7 Differential Diagnosis

The differential diagnosis of telogen effluvium in children usually includes the diffuse type of alopecia areata and loose anagen hair. In alopecia areata, the trichogram is not always helpful since telogen and dystrophic hairs are found in the hair mount. Close inspection of the scalp, face or body often reveals small patchy areas of alopecia and nail pitting. Sometimes a history of former patchy hair loss in one area of the scalp or a positive family history is found. In doubtful causes a skin biopsy is necessary, showing typical signs of alopecia areata. Loose anagen hair is easily identified in the trichogram presenting with predominantly anagen hairs and lack of telogen or dystrophic hairs.

14.3.1.1.8 Treatment

After having reversed and treated the underlying cause, hair usually regrows within the next 3 months without any additional treatment. Counseling of parents to remain patient is important to exclude any unnecessary additional treatment.

14.3.1.2 Alopecia Areata Diffusa, Totalis or Universalis

Synonyms
Pseudopelade, alopecia universalis OMIM 104000

14.3.1.2.1 Introduction

Alopecia areata diffusa is a chronic inflammatory disease characterized by acute onset of non-scarring hair loss without epidermal signs of inflammation.

14.3.1.2.2 History

For further details of history please see Sect. 14.2.1.1.

14.3.1.2.3 Epidemiology

For further details of epidemiology please see Sect. 14.2.1.1.

14.3.1.2.4 Pathogenesis

In alopecia areata, Galbraith and Pandey [18] found that the distribution of Th1/Th2 phenotypes differed between patients with the patchy form of the disease and patients with totalis/universalis disease. There was no significant difference in the distribution of the phenotypes for the second system. The results suggested genetic heterogeneity between the two forms of alopecia areata. The tumor necrosis factor alpha (TNF-α) gene is a closely linked locus within the major histocompatibility complex on chromosome 6 where this gene maps and may play a role in the pathogenesis of the patchy form of the disease. Current reports of a manifestation and progress of alopecia areata totalis and universalis in patients receiving TNF-α- blocking agents may contradict the notion that TNF-α is as central to the pathogenesis of alopecia areata as previously believed, and the role as a key target should be reconsidered [33].

14.3.1.2.5 Clinical Features

Clinical features of alopecia areata include its severe forms alopecia areata totalis and universalis. In some cases, a diffuse form may be present initially. Usually, remaining patchy lesions with non-scarring alopecia represent the diagnostic clue in these forms.

14.3.1.2.6 Pathology

In alopecia areata diffusa patchy lesions are mainly absent on the scalp, and trichogram analysis shows elevated telogen and dystrophic hairs. Thus, diagnosis is made by additional features such as sudden onset of hair loss, nail involvement, patchy hair loss in other regions of the body or a positive family history of alopecia areata. Other causes for telogen effluvium such as metabolic disorders, anemia, hormonal dysregulation (e.g., thyroid disease) should be excluded.

14.3.1.2.7 Treatment

See treatment as described in localized alopecia areata in Sect. 14.2.1.1 and Chap. 15.

14.3.1.2.8 Differential Diagnosis

Alopecia areata universalis should be distinguished from atrichia with papular lesions and congenital hypotrichosis. In alopecia areata skin is unaffected without any epidermal lesions. In difficult cases skin biopsy reveals characteristic peribulbar lymphocytic infiltrate in alopecia areata.

14.3.1.3 Loose Anagen Hair

Synonyms
loose anagen hair syndrome, loose anagen syndrome OMIM 600628

14.3.1.3.1 Introduction

The loose anagen hair syndrome (LAS) is a sporadic or familial hair disorder that primarily affects children but may occasionally be seen in adults.

14.3.1.3.2 History

More than 100 white patients with LAS have been described in the literature by Price and Gummer in 1989 [72]. The most important problem in diagnosing LAS is that the weak hair shaft–hair follicle adhesion characterizing the disorder also occurs in a small proportion of follicles of clinically unaffected individuals. This may lead to over diagnosing of LAS, particularly when the diagnosis is based mainly on microscopic than on clinical features.

14.3.1.3.3 Epidemiology

Loose anagen hair is typically diagnosed in childhood, usually after an age of 2 years, with the mean age of reported patients being 6 years. Adult cases have occasionally been described, mostly in parents of affected children.

The condition has been reported more frequently in female than in male patients (ratio, 6:1), but this may be owing to under-reporting in male patients: the most important clinical sign, the failure of hair to grow long, might not be evident in boys, who usually keep their hair short.

14.3.1.3.4 Pathogenesis

It is believed that LAS results from a premature keratinization of the inner root sheath that produces an impaired adhesion between the cuticle of the inner root sheath and the cuticle of the hair shaft. The outer root sheath–inner root sheath adhesion is involved in a number of cases [96]. Mutations in the gene encoding for the companion-layer keratin (K6HF) in some members of families with LAS have been found. The genetic basis of LAS may involve more than one gene encoding for keratins expressed in the inner root sheath or in the companion layer. Another possible candidate may be the gene encoding for the new keratin (K6IRS) specific for the inner root sheath [96].

14.3.1.3.5 Clinical Features

In LAS, anagen hairs are easily pulled from the scalp. An early age of onset is common. The majority of patients are blond girls, aged 2–5 years, but both sexes and also those with dark hair can be affected (Fig. 14.18). The hair is relatively sparse and does not grow long. Usually the hairs are not fragile and there are no areas of breakage. Three different phenotypes of LAS exist: (1) patients with type A LAS have sparse hair that does not grow long, and they often present with patches of dull, unruly hair; (2) patients with type B LAS have diffuse or patchy, unruly hair; and (3) patients with type C LAS have increased hair shedding [96].

14.3.1.3.6 Pathology

Diagnosis of LAS relies on number and percentage of hairs at the pull-test and on anagen-dysplastic hairs (anagen hairs devoid of sheath) in the trichogram. In case of LAS, pull-test reveals more than 3–10 hairs, easily and painlessly to pluck. The trichogram shows 70%–100% anagen-dysplastic (syn. loose anagen) hairs in comparison with the 10% anagen-dysplastic hairs found on the trichogram of normal adults. Slight flattening and longitudinal grooving has been noted on electron microscopy [39]. Loose anagen hair syndrome is in most cases isolated, but it also occurs in association with hereditary or developmental disorders. These include coloboma, Noonan syndrome, hypohidrotic ectodermal dysplasia, EEC syndrome, trichorhinophalangeal syndrome, nail-patella syndrome, and FG syndrome (personal observations of the authors). Patients with LAS and alopecia areata have also been reported [96].

14.3.1.3.7 Differential Diagnosis

Presence of loose anagen hairs at the pull-test or on trichogram is, however, not specific for LAS since it may also occur in healthy individuals. Trichotillomania should be excluded by clinical pattern.

14.3.1.3.8 Treatment

Parents of children should be advised to use a mild hair care routine to reduce fraction or trauma to hair, since it is easy to pull out. The length and density of hair gradually increase with age, but anagen hairs may remain loosely anchored even in adulthood [65, 72].



Fig. 14.18 Gradual hair loss was noted in a 5-year-old boy. No other anomalies of hair were found. Physical and mental development were normal and hypotrichosis simplex, localized type, was diagnosed

14.3.1.4 Hypotrichosis Simplex

Synonyms
hereditary hypotrichosis simplex, pure hypotrichosis, HTS OMIM 605389

14.3.1.4.1 Introduction

Hypotrichosis simplex is a genotrichosis characterized by two types: a hair defect limited to the scalp or affection of the scalp and body hair; both in the absence of other ectodermal or systemic abnormalities.

14.3.1.4.2 History

A localized form was first described by Toribio and Quinones in 1974 with several subsequent reports [95]. Baumer and colleagues described a non-consanguineous Italian family with hypotrichosis simplex in an autosomal-dominant pedigree pattern [8].

14.3.1.4.3 Epidemiology

Hypotrichosis is a relatively common feature of a number of complex hereditary syndromes. However, the isolated variant hypotrichosis simplex is particularly uncommon.

14.3.1.4.4 Pathogenesis

A genome wide linkage analysis resulted in a positive 2-point lod score of 3.31 at $\theta=0$ at 18p11.32-p11.23 [8].

14.3.1.4.5 Clinical Features

Hypotrichosis simplex can be divided into two main forms: generalized (or universal or total) in which the defects involve all the body hair, and localized (hereditary hypotrichosis of the scalp) in which hair loss is limited to the scalp with the rest of the pilary system being normal. Usually, children present with normal hair at birth and during the first years of life. They experience a progressive, gradual loss of scalp hair, beginning in the middle of the first decade and leading to almost complete loss of scalp hair by the third decade. A small amount of sparse, fine, short hair can remain in some children. No associated abnormalities have been reported. Phenotypic variation has to be considered (Fig. 14.18).

14.3.1.4.6 Pathology

Examination with both light microscopy and polarizing light microscopy shows dystrophic, thin hair bulbs but no structural abnormalities. Microscopic examination of a scalp biopsy specimen reveals a reduced number of hair follicles. No inflammatory infiltrates should be present.

14.3.1.4.7 Differential Diagnosis

In contrast to the total and permanent absence of hair in congenital atrichia, hair is present in hereditary hypotrichosis simplex but is diffusely thinned. Another form of isolated hypotrichosis, the Marie Unna type, is distinguished from hypotrichosis simplex by the presence of a twisting hair dystrophy. Associated ectodermal or other defects should be excluded in hypotrichosis simplex. Premature presentation of androgenetic alopecia is ruled out by trichogram or video-assisted phototrichogram showing a decreased anagen/telogen ratio in the frontal versus the occipital region.

14.3.1.4.8 Treatment

No effective treatment is available in this inherited condition.

14.3.1.5 Congenital Hypotrichia Marie Unna

Synonyms
Marie Unna hypotrichosis, Marie-Unna hypotrichosis, Marie Unna hereditary hypotrichosis, hypotrichosis of Marie Unna, hereditary trichodysplasia OMIM 146550

14.3.1.5.1 Introduction

Marie Unna hypotrichosis is a rare autosomal-dominant congenital alopecia characterized by progressive hair loss starting in early childhood.

14.3.1.5.2 History

Marie Unna is accredited with the first description in 1924 of a family with sparse or absent hair at birth, very coarse regrowth of hair in early childhood, and hair loss mainly at the vertex after puberty [5, 53].

14.3.1.5.3 Epidemiology

Marie Unna hypotrichosis is a rare autosomal-dominant condition in which abnormalities are confined to hair shaft structure and hair density. Several pedigrees have been described [108].

14.3.1.5.4 Pathogenesis

There is evidence for linkage to the disease on chromosome 8p21 close to the hairless locus. Recently, an affected family was mapped to a 17.5 cM region between markers D1S248 and D1S2345 [108].

14.3.1.5.5 Clinical Features

Affected children are born with little or no eyebrows, eyelashes, or body hair. Characteristically coarse, wiry, twisted hair develops in early childhood and is followed by the development of alopecia after puberty. The hair loss presents as an isolated feature in these patients. However, follicular keratosis and milia-like facial lesions are often found.

14.3.1.5.6 Pathology

In light microscopic or electron microscopic analysis, both torsion and longitudinal grooving of the hair shaft or pili torti are found [5].

14.3.1.5.7 Differential Diagnosis

Apart from hypotrichosis simplex, other hypotrichoses with associated defects should be differentiated. Progressive patterned scalp hypotrichosis and wiry hair similar to that seen in Marie Unna hereditary hypotrichosis differ from those of Marie Unna, including absence of signs of abnormality at birth, relative sparing of body hair, distal onycholysis, and intermittent cosegregation with autosomal-dominant cleft lip and palate.

14.3.1.5.8 Treatment

Hypotrichia Marie Unna is often aggravated at puberty, leading to scarring alopecia of variable severity [53]. No effective treatment is yet available.

14.3.1.6 Atrichia with Papular Lesions

Synonyms

papular atrichia, generalized atrichia with rickets resistant to 1,25-dihydroxyvitamin D, OMIM 209500

14.3.1.6.1 Introduction

Congenital atrichia with papular lesions is a rare, autosomal-recessive form of total alopecia and mutations in the hairless gene have been implicated in this disorder.

14.3.1.6.2 History

Atrichia with papular lesions was first described in 1954 by Damste and Prakken [28]. Attention has recently focused on this disease because of the description of several kindred with generalized atrichia associated with a mutation of the human homolog of the well-known murine hairless gene [1] (see also Chap. 6).

14.3.1.6.3 Epidemiology

A phenotypic heterogeneity in inherited atrichias caused by mutations in the hairless gene may explain the low prevalence of this disorder, considering that pathogenetic mutations in hairless gene have been found in distinct ethnicities around the world. Therefore, it is likely that congenital atrichia with papular lesions is far more common than previously thought and is often mistaken for its phenocopy, the putative autoimmune form of alopecia universalis [101].

14.3.1.6.4 Pathogenesis

The hairless gene was recently cloned and sequenced on human chromosome 8p12 and segregates with the disease in an autosomal-recessive manner [64]. A novel 11-bp insertion mutation, G202 (InsCTTCCCCCAGG), in exon 2 of the hairless gene was identified in a Pakistani consanguineous family affected by congenital atrichia. The insertion results in the expansion of an 11-bp tandem repeat, which introduces a translational frameshift leading to a downstream premature termination codon. As has been clarified, this is a non-inflammatory genetic condition with no relationship to alopecia areata, which is an autoimmune condition [101]. Mutations in the hairless gene (HR) have been found in this phenotype in both mice and humans [60].

14.3.1.6.5 *Clinical Features*

Apparently normal hairs are present at birth in most patients, but these neonatal hairs are usually shed within the first months of life and are never replaced. In individual cases, the shedding of the hair occurs during the first 2–3 years of life. At approximately 2 years of age, affected patients begin to develop multiple follicular papules and variations in the structure and morphology of the hair follicle remnants have been reported [91]. Another rare condition to consider in atrichia is rickets resistant to 1,25-dihydroxyvitamin D. These patients present with loss of some or all scalp, body, and facial hair (with or without loss of eyelashes), typical within the first 15 months of life [42].

14.3.1.6.6 *Pathology*

Histologic examination of affected scalp skin shows the absence of mature hair follicle structures and keratinous cysts in the dermis. Children resistant to 1,25-dihydroxyvitamin D have clinical and radiological signs of rickets, such as bowed limbs, extremity fractures, and diffuse osteopenia, accompanied by laboratory abnormalities including marked hypocalcemia with secondary hyperparathyroidism and elevated levels of 1,25-dihydroxyvitamin D and alkaline phosphatase.

14.3.1.6.7 *Differential Diagnosis*

Between the ages of 2 and 26 years, patients develop numerous keratinous, papular cysts resembling milia on the head, upper torso, and extremities, distinguishing them from patients with alopecia totalis/alopecia universalis. In the first months of life, it may be difficult to identify vitamin-D-resistant rickets, because clinical signs of rickets may not yet be apparent [57].

14.3.1.6.8 *Treatment*

Due to the genetic pathogenesis of the disease no effective treatment is known to induce regrowth of hairs.

14.3.2 Scarring Alopecia

Scarring alopecia in children is very rare, but should be excluded clinically in cases of localized alopecia by dermascopic evaluation of the scalp. In case a scarring alopecia is suspected a skin biopsy is useful to specify the cause.

14.3.2.1 Keratosis Follicularis Spinulosa Decalvans

Synonyms
keratosis pilaris atrophicans, keratosis follicularis spinulosa decalvans cum ophiasis OMIM 308800

14.3.2.1.1 *Introduction*

Keratosis follicularis spinulosa decalvans is a rare, X-linked disorder affecting both the skin and eyes [3]. In the case of follicular hyperkeratosis, variable degrees of inflammation and secondary atrophic scarring are characteristic features of keratosis follicularis spinulosa decalvans.

14.3.2.1.2 *History*

Keratosis follicularis spinulosa decalvans is a rare disorder characterized by widespread keratosis pilaris and scarring alopecia of the scalp and eyebrows. Onset of the skin disease is in early childhood but with scalp involvement occurring in the teen years [6]. During infancy, keratosis pilaris begins on the face and, by childhood, progresses to involve the trunk and extremities. Sometime during childhood or up to the early teenage years, a cicatricial alopecia of the scalp and eyebrows develops and is the hallmark of this disorder [76]. Ocular abnormalities and palmoplantar keratoderma are less frequent associations.

Siemens (1925) described [84] two families with X-linked inheritance of keratosis follicularis spinulosa decalvans. According to information available, one family was from Bavaria and the other from the Netherlands. Siemens personally investigated two members of the Dutch family on the invitation of Lameris, who had reported the cases as ichthyosis follicularis. Two weeks after his visit to Lameris, Siemens encountered the index cases of the Bavarian family. The ophthalmologic features of the Lameris family were reported by Rochat in 1906 [66].

14.3.2.1.3 *Epidemiology*

X-linked dominant inheritance has been reported in several families with keratosis follicularis spinulosa decalvans, with men more severely affected. Genetic studies on a large Dutch and British pedigree have demonstrated linkage to Xp22.13-p22.2 [69].

14.3.2.1.4 Pathogenesis

In keratosis follicularis spinulosa decalvans, the linkage to Xp22.13-p22.2 has previously been reported [69]. Analyses of other families do not support X-linked inheritance, thus suggesting genetic heterogeneity. An inflammatory follicular process results in destruction and scarring.

14.3.2.1.5 Clinical Features

Keratosis follicularis spinulosa decalvans is characterized by follicular hyperkeratosis of the skin and corneal dystrophy. Typically, keratosis pilaris begins on the face in infancy and may progress to become more widespread on the trunk and limbs. Affected males show thickening of the skin of the neck, ears, and extremities, especially the palms and soles. Scarring alopecia of the scalp subsequently occurs in childhood or early adolescence. Alopecia may be patchy or diffuse (Fig. 14.19). Loss of eyebrows, eyelashes may be present. Rarer features include palmoplantar keratoderma, atopy, photophobia, and ocular abnormalities, in particular corneal dystrophy. An ophthalmological evaluation is required to examine thickening of the eyelids with blepharitis and ectropion, and corneal degeneration.

14.3.2.1.6 Pathology

The characteristic histological findings are dilatation of the hair follicle with keratin plugs, a perifollicular and perivascular lymphocytic infiltrate, and scarring. Stains should be negative for bacteria and fungi.



Fig. 14.19 Keratosis follicularis decalvans was found in a 15-year-old girl presenting with scarring alopecic patches on the scalp. Follicular hyperkeratosis is seen in the border of the alopecic area

14.3.2.1.7 Differential Diagnosis

Acne keloidalis nuchae may be considered in the occipital scalp and posterior neck region, characterized by folliculocentric pustulopapules that scar, resulting in keloidal plaques. This typically affects adolescent men with dark skin. Acne keloidalis nuchae is classified under the mixed group of primary cicatricial alopecia, with an initially neutrophilic inflammatory infiltrate and a latter infiltrate consisting of a mixture of lymphocytes and plasma cells, with the formation of foreign body granulomata [37].

14.3.2.1.8 Treatment

Effective therapeutic options for this disease are not known, but there have been anecdotal reports of the efficacy of oral etretinate and isotretinoin. Oral isotretinoin at 0.25 mg/kg daily can improve inflammation.

14.3.2.2 Pseudopelade of Brocq

Synonyms
pseudopelade Brocq, Brocq's pseudopelade OMIM NA

14.3.2.2.1 Introduction

The term pseudopelade describes a pattern of alopecia that is different to the classic "pelade" found in nonscarring alopecia areata. Pseudopelade is characterized by diffuse patches of scarring alopecia of unknown origin [17].

14.3.2.2.2 History

The term pseudopelade was introduced by Brocq in 1905 [17]. Later reports defined it as an end-stage or clinical variant of various forms of scarring alopecia. A distinct entity or a "primary" form of pseudopelade may exist, but this has yet to be established with certainty.

14.3.2.2.3 Epidemiology

Pseudopelade is a pattern of alopecia that is rarely encountered and is very rare in children; familial occurrence has been reported [21].

14.3.2.2.4 *Pathogenesis*

The pathogenesis of pseudopelade Brocq is unknown. Assuming that pseudopelade Brocq is an end-stage of other forms of scarring alopecia, the inflammatory infiltrate as seen in discoid lupus erythematosus or lichen planopilaris could cause disturbance of the stem cell area and lead to permanent destruction of the hair follicle [92].

14.3.2.2.5 *Clinical Features*

Typically, discrete asymptomatic areas of alopecia are found on the scalp. In general, the disease is slowly progressive. Frequently, patches of scarring alopecia like "footprints in the snow" are found. Alopecic patches are irregularly shaped, widely distributed, and clustered on the scalp. The individual lesion is porcelain white and slightly atrophic.

14.3.2.2.6 *Pathology*

The histopathological findings of pseudopelade have yet to be clearly defined. Biopsy shows reduced numbers of hair follicles and sebaceous glands, in some cases a sparse lymphocytic infiltrate is present.

14.3.2.2.7 *Differential Diagnosis*

With regard to the scarring character of pseudopelade, it is important to bear this diagnosis in mind whenever one encounters a child with patchy or diffuse alopecia. Other forms of scarring alopecia such as lichen follicularis or cutaneous lupus erythematosus show clinically perifollicular erythema and scaling. Traumatic induction or aplasia cutis congenita are sharply demarcated and do not resemble the classical description "like foot prints in the snow" as found in pseudopelade.

14.3.2.2.8 *Treatment*

There is no effective therapy to treat pseudopelade. If pseudopelade shows progression correlated with histopathologic mild lymphocytic infiltrate, a topical treatment with corticosteroid solution may be tried.

Summary for the Clinician

Age of onset, history, and associated symptoms are important factors to be considered. First, the *age at onset* may help to further narrow the disease. The most frequent causes of hair loss in 1- to 3-year-old children are hair shaft defects with increased fragility, alopecia areata, and mycotic scalp manifestations (tinea capitis). Amongst older children (aged 4–11 years), the most significant causes are alopecia areata, loose anagen hair, artificial hair loss (trichotillomania, traction alopecia), and hair loss of infectious origin (microsporia, tinea capitis, folliculitis). Amongst adolescents (aged 12–18 years), alopecia areata and early onset of androgenetic alopecia represent the most frequent reasons for a consultation (Table 14.1; [71]). The following compilation comprises the most important differential diagnoses, according to the age at onset and their clinical characteristics in children. This chapter does not emphasize hair loss in adolescents, e.g., androgenetic alopecia (see Chaps. 9, 10), although it is mentioned in Table 14.1 for the sake of completeness.

As a second step, further diagnostic clarification of hair diseases in children is based on the patient's personal and family history, a thorough clinical examination, as well as general and specific diagnostic procedures. The patient's history provides information about the age of the patient when the initial manifestation occurred, the subsequent development of the disease and associated symptoms. In addition, the family history may illustrate the occurrence of the disease within members of that family. Important features of genotrichoses are the associated symptoms and anomalies; thus, the dermatologist or pediatrician should focus his or her attention on the evaluation of physical and mental development, and also take into consideration noticeable psychological problems of the child.

On the one hand, the clinical assessment should consider whether the hair loss (effluvium) is localized or diffuse and whether it is scarring or non-scarring (Table 14.2). On the other hand, it is crucial to determine whether any hair shaft defects simulating hair loss (Table 14.3) are present, or if decreased hair density (hypotrichosis, atrichia, and alopecia) is a result of prior shedding. Accordingly, a thorough clinical examination of the entire head and body is necessary, in order to evaluate the pattern of hair growth, variances in nail growth, impaired vision, defective hearing or dysfunction of

perspiration. Furthermore, the scalp should be examined regarding signs of inflammation, dandruff and scaling, scarring, edema or other skin symptoms. In addition, the hair quality, color, roughness, and tendency to breakage should be critically evaluated.

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Chapter 15

Alopecia Areata

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15

Synonyms
pelade

Key Features

- Alopecia areata (AA) is a reversible, initially patchy hair loss most commonly involving the scalp although other regions of the head, including eyelashes and beard, may also be affected. The disease may sometimes lead to complete baldness of the scalp (alopecia areata totalis) or of the entire body (alopecia areata universalis).
- The course of AA is usually characterized by phases of acute hair loss followed by spontaneous hair regrowth and waxing and waning of the lesions. However, in severe forms hair loss can persist for many years or even life.
- Typical nail changes of AA are pitting, transversal grooves, red spotted lunulae or trachyonychia.
- Histopathological features of AA include perifollicular and intrafollicular lymphocytic infiltrates involving only anagen hair follicles with subsequent miniaturization of these structures.
- Alopecia areata is regarded as a T-cell-mediated autoimmune disease of the hair follicle that is mediated by $CD4^+$ and $CD8^+$ T-lymphocytes. As with other autoimmune diseases, AA most likely has a polygenic character, where susceptibility is dictated by several major genes and the phenotype may be modified by numerous minor genes.
- The most effective treatment for severe AA is the application of a contact sensitizer, while limited AA can be treated by intralesional corticosteroids or clobetasol propionate 0.05% ointment under occlusion. Pulse therapy with systemic corticosteroids or psoralen UV A (PUVA) is often used but neither has yet been proven in controlled studies to be effective in AA.

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15.1 Introduction

Alopecia areata (AA) is a common disease of men, women and children. Even though it is potentially always reversible, it may sometimes lead to complete baldness of the scalp or of the entire body and, in severe forms, hair loss can persist for many years or even life. Hence, AA is psychologically and socially disturbing for patients and a therapeutic challenge for the dermatologist.

15.2 History

Alopecia areata has been known about for at least 2000 years; it was first described in the year 57 AD.

15.3 Epidemiology

There is a lifetime risk for AA of 1.7% in the general population [72]. The disease affects both sexes with a slight predominance of females and may occur at all ages [75, 81, 93]. Even though there is a relatively high percentage of patients who have their first episode of AA before they are 20 years old (between 27% and 69.9% in different studies), children as young as 4 months and adults in their late seventies have been described to develop AA [75, 81, 93].

15.4 Pathogenesis

15.4.1 Genetics

The genetics of an individual may play roles at multiple levels in the development of AA. While the presence of defective genes is possible in AA, it seems unlikely given that most other autoimmune diseases have not been shown to involve specific gene mutations. Rather, the primary mode of genetics' contribution to AA seems to be the existence of functional gene alleles that code for increased disposal of the immune system towards autoimmunity, and specifically towards AA development [4]. Major histocompatibility complex (MHC) gene alleles have been characterized that have a more favorable conformational structure for the presentation of antigens involved in autoimmunity. Other gene alleles may encode in favor of a pro-inflammatory state or they may be less capable of regulating inflammation. The genetic makeup of an individual is constant, but AA expression is variable over time. It seems likely that variation in the patient's environment, and a complex interplay between environment and genes determine disease onset and expression for each individual [5].

Several studies suggest that AA has a genetic basis [88]. Alopecia areata in monozygotic twins with similar times of onset or similar hair loss patterns has been reported [2, 78]. Families with several generations of AA-affected individuals also suggest that AA may be a genetically determined disease [38, 76, 87]. There is a higher incidence of AA in genetically related individuals. Typically, 10%–20% of patients with AA indicate at least one other affected family member, whereas the lifetime risk of AA expression in the general population has been suggested to be 1.7% [72]. A recent study by Blaumeiser et al. [6] showed that estimated lifetime risks were 7.1% in siblings, 7.8% in parents, and 5.7% in offspring. The risk in second-degree relatives is slightly higher than the reported population risk. Age at onset in index patients and that in first-degree relatives were significantly correlated. This suggests that at least some people are genetically predisposed to develop AA. The triggers for the onset of AA may be environmental, but the resistance of the AA lesion to treatment, its persistence and regression, and its extent over the body may be influenced by the presence and interaction of multiple genes.

A strong association has been observed between AA and trisomy 21 (Down's syndrome). From 1000 patients and 1000 control subjects, Du Vivier and Munro observed 60 cases of trisomy 21 individuals with AA versus 1 control [16]. Carter and Jegasothy identified 19 cases of AA in 214 trisomy-21-affected patients and the statistical relationship is further supported in other

studies [9, 92]. The genetic mutation for autoimmune polyendocrinopathy syndrome type 1 (AIRE, autoimmune regulator gene) is also associated with a 29%–37% prevalence of AA [5]. These studies suggest that candidate gene loci for AA susceptibility may be on human chromosome 21.

Associations of AA with other autoimmune diseases have also been reported. Between 7% and 27% of AA-affected patients may also have a disease, including goiter presence, myxedema and Hashimoto's thyroiditis [71, 77]. Co-expression of vitiligo and AA has also been reported at between 4% and 9% [63]. However, the statistical significance of these disease associations when compared to appropriate control populations has been disputed elsewhere. Numerous case reports detail the concordant presence of AA with other autoimmune diseases, such as diabetes and myasthenia gravis, although the statistical significance is unknown [49].

Alopecia areata has been proposed to be an autoimmune disease based on several indirect observations in humans and animal models of the disease [51]. Genetic influence has been clearly demonstrated in most other autoimmune diseases and one would expect that AA is no exception. Alopecia areata is clearly a complex disease; it does not segregate according to the rules of Mendelian inheritance [88]. As with other autoimmune diseases, AA most likely has a polygenic character, where susceptibility is dictated by several major genes and the phenotype may be modified by numerous minor genes.

15.4.1.1 Rodent Models

Two rodent models have been developed and characterized for use in AA research: the Dundee experimental bald rat (DEBR) and the C3H/HeJ mouse [59, 62]. Alopecia areata in both rodent models has been shown to be an autosomal polygenic trait with partial phenotype penetrance by analysis of breeding programs. To identify genes involved in the hair loss, mice were analyzed for linkage in a genome-wide scan with microsatellites. Using various tests, hints at linkage on chromosomes 5 and 8 with non-parametric Z scores of 2.4 ($p<0.008$) and 2.5 ($p<0.006$), respectively, in mice with an AA phenotype were obtained. The Cochran-Armitage test showed slight association for markers on chromosome 14 ($p<0.02$).

C3H/HeJ mice have existed as a unique inbred strain at the Jackson Laboratory since 1947, but onset of the AA phenotype was first observed in several individuals of a C3H/HeJ mouse colony in 1993. The mouse breeding pattern permitted tracing the genetic history of the affected mice to a single breeding pair at generation F198, suggesting a genetic modification of the strain in one parent. The segregation pattern of phenotypes suggests that AA in laboratory mice is under the control of one or more dominant gene alleles. A preliminary backcross study between C3H/HeJ mice and C57BL6/J mice suggested a tentative locus for susceptibility on mouse chromosome 6 (37cM, 1 recombinant/24 alleles with D6MIT230 is 4.2 cM, $p=3{\cdot}10^{-6}$, 95% confidence interval of the distance is 0.1–21.1 cM) [50]. Within this region are numerous immunoglobulin genes, a gene for cytokine transforming growth factor alpha (TGFα), as well as genes for the lymphocyte surface markers CD8 and Ly36. The mouse locus corresponds to human chromosome region 2p13. Thus, this region may be worthy of close attention within a genome-wide screen.

C3H/HeJ mice cross bred with C57/BL6J mice yield 7% of affected F1 generation mice and intercross studies with C57BL6/J mice are in progress with up to 13 candidate gene loci under investigation supporting the hypothesis that AA is a polygenic disease [80]. Using various tests, hints at linkage on chromosomes 5 and 8 with non-parametic Z scores of 2.4 ($p < 0.008$) and 2.5 ($p < 0.006$), respectively, in mice with an AA phenotype were obtained. The Cochran-Armitage test showed slight association for markers on chromosomes 14 ($p < 0.02$).

15.4.1.2 Humans

15.4.1.2.1 HLA Genes

It has been suggested that the HLA gene products, the MHC antigens, could be important for the presentation of an unknown AA antigen. Aberrant expression of MHC proteins within AA-affected hair follicles is frequently found, but the question of its true significance remains unsolved. There are many more alleles that code for other factors within, and outside of, the immune system that may be vital in the development of AA.

Human leukocyte antigen (HLA) genes on human chromosome 6 code for the MHC proteins that are important in presentation of antigens and self-recognition by immune cells. The MHC class I antigens comprise the HLA-B, HLA-C and HLA-A loci in this order. MHC class II is coded by genes in the HLA-D region that is subdivided into gene clusters HLA-DP, HLA-DQ, and HLA-DR. MHC class I antigens are expressed on almost all nucleated cells. $CD8^+$ lymphocytes have the capacity to recognize cellular antigens presented in association with MHC class I via their T cell receptors. In contrast, MHC class II antigens are normally expressed on antigen-presenting cells (APCs), such as macrophages and Langerhans' cells, and expression may be induced on other nucleated cells during inflammatory processes such as AA. $CD4^+$ lymphocytes may recognize antigen

plus MHC class II complexes on APCs. Different MHC proteins may have superior presenting properties for particular antigens compared to other MHC complexes and consequently some complexes of antigen plus MHC will be more effective in their activation of lymphocytes than others. In part, this may determine the ability of lymphocytes to respond to the hair follicle antigen(s) targeted in AA and may define how potent an immune response against a particular antigen will be.

Genetic research into other autoimmune diseases has shown HLA-encoding alleles to segregate with specific disease phenotypes. However, inconsistent results have been found with analysis of HLA class I haplotypes of the A and B series and AA. Some studies report statistically significant associations, but other studies found no HLA class I association [95]. Genetic analysis studies in AA have primarily focused on the HLA-D genes (MHC class II encoding) as the most likely region for genes that regulate susceptibility to, the severity of, or resistance to disease [17]. Consistent associations have been observed between class II haplotypes and AA (Table 15.1). The current consensus is that AA in humans has a genetic basis, but is not always in a familial aggregation [88].

A very recent [60] genome-wide linkage study used a panel of 324 microsatellite markers on a cohort of 177 DNA samples from 22 multiplex AA pedigrees, comprised of 78 affected and 69 unaffected family members. Statistical analyses demonstrated a LOD score of 4.831 for the Affected Sib Pair method and a MAX-HLOD score of 3.554 at marker D6S1009 on chromosome 6q23.3. Other loci on chromosomes 10, 16, 18 also showed suggestive evidence for linkage (LOD 1.5) to AA. In conclusion, significant evidence of at least one genetic determinant of AA was found on chromosome 6q23.3, outside the region of the HLA gene cluster. In addition to HLA molecules, non-HLA molecules including MHC class I chain-related gene A (MICA), a stress-inducible antigen, are also associated with several autoimmune diseases. The results suggested that MICA is both a potential candidate gene and part of an extended HLA haplotype that may contribute to the susceptibility to and severity of AA.

Table 15.1 Associations of HLA and of non-HLA genes with AA

Gene		Association with
HLA	HLA-A2, B40, Aw32, B18	AA [3]
	HLA-B12 in Finnish patients	
	HLA-B18 in Israelis	
	B13 and B27 in Russians	
	DR4, DR59, DR5, DR6, DR7, broad antigen DQ3	AA [3, 28, 60, 62, 82]
	DRB1*1104 (DR11)	
	DQB1 alleles, DQB1*302, DQB1*601, and DQB1*603	
	Allele DRB1*0401 (DR4)	AAT / AAU [12]
	DQB1*0301 (DQ7 by serology)	
	MICA(*)6	AA [4]
	HLA-DQ1-DR6-MICA(*)5.1	
	HLA-DQB1*0201-DR3-MICA(*)5.1	
	MICA(*)5.1	AAP[4]
Non-HLA	2 of a 5-allele polymorphism for the IL-1rn gene	44% in AAP, 66% in AAT, 77% in AAU [82]
	Genes for immunoglobulin heavy (Gm) and light (Km) chain	AA [25, 27]
	TNF-α gene polymorphisms	AA [14, 26]
	Notch 4 gene	Severe AA [57]

15.4.1.2.2 Non HLA Genes

The HLA gene region is likely to be only one of several gene loci involved in AA, but limited research has been conducted in other areas of the genome. One investigation has shown an association between AA and allele 2 of a 5-allele polymorphism for the IL-1rn gene on human chromosome 2 that codes for the interleukin-1 (IL-1) receptor antagonist [82]. Results indicated that allele 2 was present in 41% of controls compared to 44% of individuals with patchy AA, 66% of those with alopecia totalis, and 77% of individuals with alopecia universalis [82]. Allele 2 is known to influence IL-1β production. Galbraith et al. identified the IL-1β-1,2 genotype as significantly increased in frequency for individuals with extensive but not patchy AA, further suggesting that the severe form of disease may be associated with increased IL-1β production [28].

Genes for immunoglobulin heavy- (Gm) and light- (Km) chain genotypes on human chromosome 14 have also been implicated in AA susceptibility [25, 27] with the suggestion that IL-1β (IL-1 β-1,2) and light chain (KM-1,3) genotypes may interact to increase AA susceptibility [28]. Tumor necrosis factor alpha (TNFα) gene polymorphisms, or adjacent genes in the HLA region may also influence AA susceptibility [14, 26]. Involvement of all these gene loci, as susceptibility or severity-modifying genes, is consistent with an autoimmune pathogenesis of AA.

In addition it was found that AA is increased to more than 30% in autoimmune polyendocrinopathy candidiasis ectodermal dysplasia syndrome (APECED), a recessive condition resulting from a mutation of the autoimmune regulator (AIRE) gene on chromosome 21q22.3. Aire protein is thought to have transcriptional regulatory activity but its role is not well defined at present. On screening the AIRE coding sequence, Tazi-Ahnini et al. [83] identified 20 variants. The frequency of the rare allele (961G) was 0.08 in the controls and there was a significant increase to 0.13 in AA overall and 0.20 in severe disease (alopecia universalis). These results could provide a rational explanation for the unusually high frequency of AA in APECED patients, supporting the concept of AA as an autoimmune disease. However, another group [68] attempted to replicate these finding using a case–control sample of Belgian-German origin (273 patients and 283 controls). Despite adequate power, this study did not support a significant association with the risk allele in the AA patient sample. This remained the case when the sample was stratified according to severity and family history of disease. Therefore, the importance of the AIRE gene in AA is open to question.

In addition some associations of severe AA have been linked to the polymorphisms in Notch4-gene ($p<0.001$ for NOTCH4:1297T) [57].

15.4.2 Immunology

The most popular explanation for AA disease development involves the principle of autoimmunity. It is generally accepted that in AA hair-follicle-associated antigens activate an inappropriate immune response, targeting anagen-stage follicles which leads to disruption of hair fiber growth. More recently, with the aid of several animal models of AA, indirect, functional evidence has been produced to show that the immune system dominates in determining the expression of AA [57]. But the key question, namely whether AA is an autoimmune disease, remains to be answered. While the evidence in support of such an autoimmune scenario is compelling, AA is yet to be proven as a true autoimmune disease. The primary requirement is to define the antigen target(s) of attack in AA as self antigens derived from the hair follicle unit. The source of antigenic targets has been variously suggested to be hair follicle melanocytes, keratinocytes, and dermal papilla cells, but as yet there is no concrete proof of specific targeting of these cell types [23]. Given the range of AA phenotype presentations, it may be that different degrees and patterns of hair loss correspond to the targeting of different antigens. In addition, there may be more than one antigen target involved in an individual's expression of AA due in part to the phenomenon of epitope spreading. However, it is anticipated that a few key antigen targets could explain the variable disease phenotype defined as AA.

15.4.2.1 Susceptibility Modifying and Causal Factors in AA

The onset of AA probably requires input from multiple factors that determine the physical and biochemical status of both the immune system and hair follicles. Essentially, these can be classified as: (1) genetic susceptibility, resistance, and severity modifying factors and (2) environmental contributors to disease susceptibility, resistance, and severity. Among these environmental factors, stress has been suggested as a potential instigator of autoimmune diseases possibly through glucocorticoid modulation of pro-inflammatory cytokine expression [19]. Stress has also been postulated to have an influence on AA development although the evidence is only circumstantial [13, 42]. Evaluative studies on a mouse model of AA showed significant changes in stress hormones and receptors as a consequence of AA expression, suggesting that the development of autoimmunity may impact on stress responses in affected individuals. Thus the relationship between stress and AA may be a two-way street and while stress may contribute to the expression of AA, AA in turn can modulate stress responses.

Other promoters of the immune system and autoimmune disease may include hormonal fluctuations.

Onset of AA is sometimes associated with hormonal changes during pregnancy suggesting a capacity to alter susceptibility to disease onset. In a mouse model of AA, estrogen increased the rate of AA expansion over the skin while androgen supplementation increased resistance to the development of AA [53]. While the data are limited, there does seem to be a hormonal influence on AA expression probably via modulation of immune system activity. Experimentally in animal models, even dietary intake can play a role in susceptibility to AA expression [55]. In principle, one or more of these factors may modulate the immune system in AA, but in practice little is known about the effects of environmental stimuli on AA in humans.

15.4.2.2 Disease Activation Mechanisms in AA

The primary disease-activation mechanism by which AA develops has not been identified. There are, however, multiple hypotheses as to how AA may be activated and progress in a susceptible individual.

It is possible that while inflammation is involved in AA, the immune system's action is secondary to hair follicle dysfunction [7, 31]. Dysregulation of hair follicle growth and cycling may have an impact on the growth of hair fiber. Secondary to this dysfunction, aberrant expression of normal antigens, or the expression of abnormal antigens, may occur in the affected hair follicles. This in turn could activate the immune system resulting in secondary inflammation. While a dysfunction in AA-affected hair follicles is quite possible, recent research suggests that overt hair loss is largely under the control of the immune system. Without immune cells, particularly T lymphocytes, AA does not develop in animal models [48].

We still do not know the event that precipitates expression of the disease phenotype, but one hypothesis suggests that AA develops in susceptible individuals as a result of a failure in hair follicle immunoprotection. Putatively, hair follicles are immune privileged sites. In the anagen phase of hair follicle growth, no Langerhans' cells can be detected in the two-thirds of hair follicles proximal to the hair bulb. Follicles are also devoid of Class Ia MHC antigens in the proximal hair follicle epithelium. Moreover, NK cells, CD4+ T-cells and CD8+ T-cells are not observed in the lower portion of the proximal hair follicle and hair bulb. In addition, immunosuppressive cytokines such as TGF-β1 and alpha melanocyte-stimulating hormone (α-MSH) are generated locally, which may further hinder MHC class I expression in anagen-stage hair follicles [67]. A failure in immune privilege need not affect hair follicle growth directly, but the presentation of normally sequestered hair follicle antigens to the immune system could result in inflammation acting on affected hair follicles and ultimately causing hair loss. Some have suggested a loss of immune privilege may be the primary initiating event for AA. However, in a mouse model of AA, where AA is transferred from affected to unaffected mice by skin grafting, injury to follicles through the sham grafting of normal skin and the induction of MHC expression in damaged follicles does not induce AA [48].

Though anagen-stage hair follicles are regarded as immune-privileged sites, follicle immunoprotection is likely to be only transient due to the nature of the hair follicle cycle. Regression of the hair follicle in catagen involves significant apoptosis and remodeling of the transient portion of the hair follicle. Immune cells, candidate APCs, infiltrate around catagen-stage hair follicles [66]. This normal process of hair follicle cycling may constantly expose the immune system to low levels of hair-follicle-derived antigens. Autoimmune disease is not regarded as an all or nothing event. Autoreactivity is a progressive scale of response to self antigens with a threshold level above which overt autoimmune disease is induced [52]. An example of this may be the low level of hair-follicle-specific antibodies found in some humans and animal models in the absence of overt AA [84]. Skin dendritic cells are capable of presenting apoptosis-derived antigens. If catagen regression becomes disordered and the immune cell infiltrate associated with catagen co-expresses antigenic peptides plus co-stimulatory molecules, antigen presentation to the immune system might breach the threshold for the onset of overt AA [43].

As alternatives to the folliculocentric hypotheses of AA activation, a scenario based purely on the immune system is possible. For autoimmune disease to occur, the immune system must contain cells reactive to self antigens. In individuals not susceptible to autoimmunity, reaction against self antigens is held in check by clonal deletion of self-reactive lymphocyte clones, primarily in the thymus. However, not all self-reactive lymphocyte clones are successfully deleted and some will reach the peripheral system. Here, such self-reactive cells are regulated by mechanisms of anergy or active suppression of activity via immune system regulatory mechanisms. Should thymic education be incomplete, or the regulatory mechanisms of the peripheral immune system fail, self-reactive cells may be free to target hair follicles resulting in AA. In a mouse model of AA, regulatory cell numbers are depressed as AA develops [96].

A variety of potential mechanisms may underlie the onset of AA [57]. Current research with animal models suggests that AA is a largely self-contained disease cycle involving four key events: (1) failure of the im-

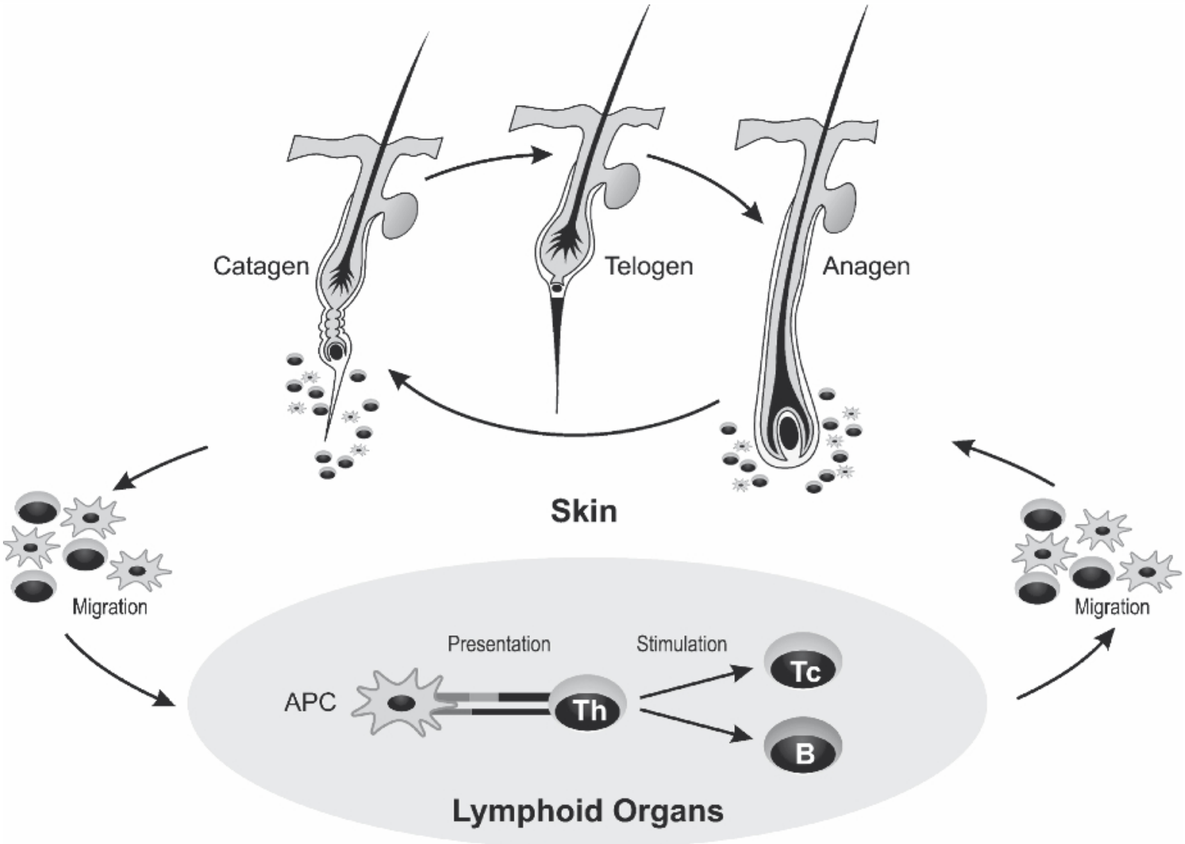


Fig. 15.1 Alopecia areata (*AA*) disease cycle. Inflammatory cells, including professional antigen-presenting cells (*APC*), are challenged in the skin with hair follicle antigens. Antigen-loaded APCs and activated cells migrate to draining lymph nodes and other organs including the spleen. Antigen presentation and the expression of pro-inflammatory cytokines initiate the activation and clonal expansion of hair-follicle-reactive lymphocytes. Activated cells migrate to the skin, surrounding anagen-stage hair follicles and inhibiting hair growth

mune privilege of any putative anagen-stage hair follicle and exposure of hair follicles located in regions of AA, inciting epitopes to the immune system; (2) antigen presentation, co-stimulation, and activation of responsive lymphocytes by APCs; (3) activated inflammatory cell migration to, and infiltration of, hair follicles; and (4) the subsequent disruptive actions of the inflammatory cell infiltrate on the hair follicles and the release of more hair follicle antigens to perpetuate the disease cycle (Fig. 15.1).

15.4.2.3 Modes of Immune System Action on Hair Follicles Leading to Hair Loss

Research has suggested a variety of mechanisms by which the immune system may act on hair follicles and promote AA (Table 15.2). Both humans and animal models have been shown to produce autoantibodies against hair follicle antigens. Tobin [84] demonstrated production of antibodies with heterogeneous targeting of hair follicle structures, and similar heterogeneity of morphological targeting has been found in mouse and rat models of AA. Trichohyalin and specific keratins have been defined as targets for some of the antibodies. However, the diversity of autoantibody production with no consistent structure targeting observed in serum samples from different patients suggests that autoantibodies are not the dominant factor in AA development. Time line evaluation studies on a mouse model for AA indicated that cellular targeting of the hair follicles occurs prior to an upregulation in genes associated with antibody production [8]. In addition, transfer of serum from AA patients to human skin grafted to severe combined immunodeficient (SCID) mice failed to regenerate the disease phenotype [29]. Though it seems unlikely that autoantibodies are the primary mediators of AA, they may still play a secondary role accentuating the chronic disease

Table 15.2 Evidence in support of AA as an autoimmune disease

Circumstantial evidence (proven)	Folliculocentric, primarily lymphocytic, inflammation
	Increased cell proliferation and activation in lymphoid organs
	Hair follicle antigen-specific autoantibody production
	Pro-inflammatory cytokine expression in the skin
	Expression of endothelial pro-inflammatory markers
	Aberrant MHC class I and class II expression in hair follicles
	Bias in genetic MHC haplotypes associated with AA expression
	Response to immunomodulatory treatments
Indirect evidence (proven and theoretical)	Multiple spontaneous mammalian and avian conditions with equivalence to human AA
	Induction of disease possible with hair follicle antigens in disease models
	Transfer of disease possible with isolated cell subsets in disease models
Direct evidence (theoretical)	Pathological changes consistent with AA at the site of localized introduction of cell subsets
	Demonstration of immune reactivity to self hair follicle antigens in humans
	Reactive self antigens present in all cases of AA
	Transfer of disease between humans with transfer of hair follicle antigens
	Transfer of disease between humans with transfer of activated autoreactive lymphocytes/antibodies

state and their investigation may provide clues as to the antigenic targeting of T lymphocytes.

In most autoimmune diseases and animal models of autoimmune disease, lymphocytes have been shown to be primary disease mediators. Typically, $CD4^+$ lymphocytes have been identified as the primary pathogenic cell population with the ability to transfer many autoimmune diseases. However other lymphocyte subsets, including $CD8^+$ cells, have also been shown to be important in disease pathogenesis. The predominantly $CD4^+$ and $CD8^+$ lymphocyte inflammation of hair follicles in AA suggests that these cells are the primary motivators of the disease phenotype. Depleting inflammatory cells with various immunosuppressive therapies supports the general view that these cells are the key to hair growth inhibition in AA [21]. In rodent models, the selective removal of specific $CD4^+$ or $CD8^+$ cell subsets using monoclonal antibodies has been shown to permit hair regrowth [54].

Cell subset transfer studies have further characterized the importance of $CD4^+$ and $CD8^+$ lymphocytes in AA. Human AA-affected, skin-derived lymphocytes have been shown to re-induce inflammatory hair loss in xenografts of previously AA-affected skin grafted to SCID mice. Separation of $CD4^+$ and $CD8^+$ cell subsets and their transfer to this model suggested that each cell type was not capable of re-inducing hair loss on its own, but in combination hair loss redeveloped [30]. In the C3H/HeJ mouse model of AA subcutaneous injection of $CD8^+$ cells led to the rapid development of localized hair loss at the site of injection, but with no further progression of the disease. In contrast, injection of $CD4^+$/$CD25^-$ cells resulted in limited localized hair loss but AA did develop in multiple patches away from the site of injection [56]. Thus, it is the $CD4^+$/$CD25^-$ cell population in the C3H/HeJ mouse model that retains the capacity to transfer the AA phenotype to naïve hosts and most likely promotes AA via promotion of APC activity and subsequent stimulation of hair follicle autoreactive $CD8^+$ cells.

15.4.2.4 Modes of Hair Follicle Response to Immune Activity Leading to Hair Loss

The onslaught of inflammatory cells in AA induces a response from hair follicles that ultimately leads to

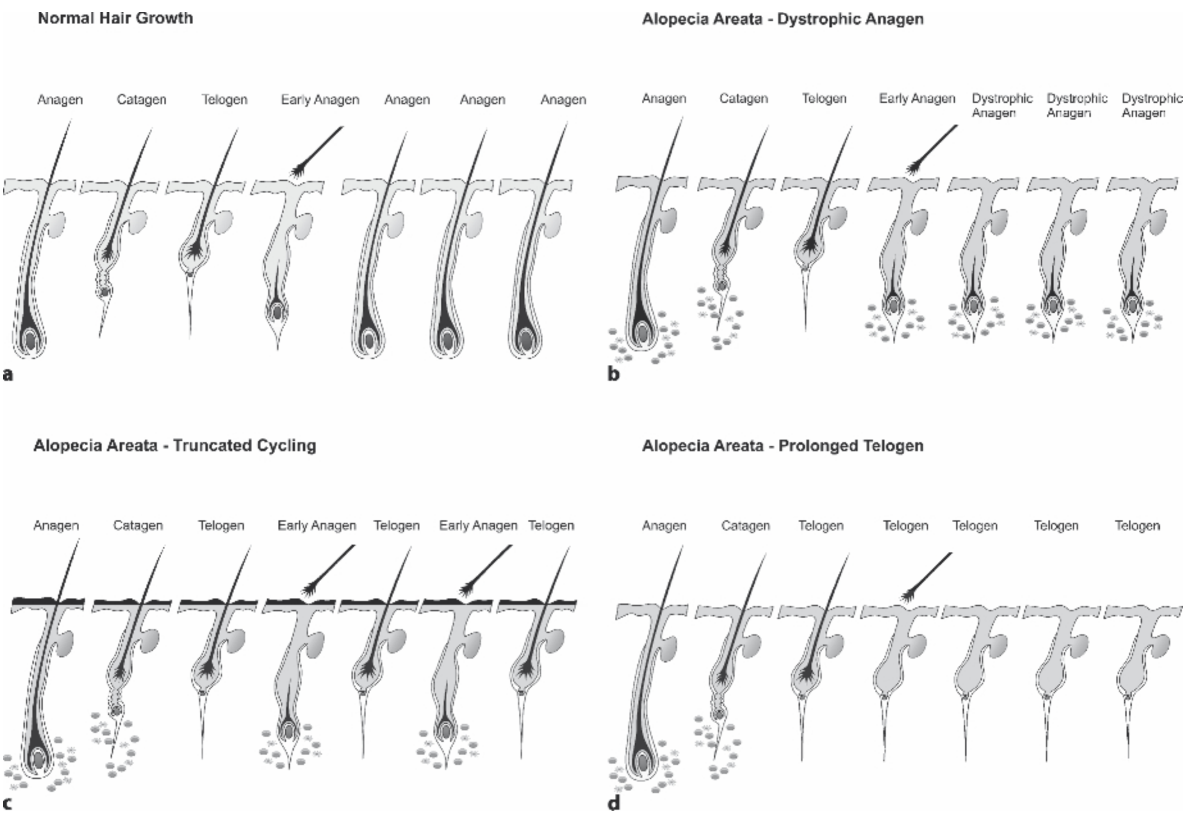


Fig. 15.2a–d Hair growth cycle changes in AA. Some argument persists in how hair loss is achieved in AA. Several possible outcomes in response to follicular targeting by activated inflammatory cells may occur. As compared to a normal hair growth cycle shown as a series of hair follicle changes at sequential time points (**a**), AA-affected hair follicles may attempt to maintain an anagen state but only achieve a dystrophic anagen state (and in chronic AA, a miniaturized dystrophic anagen state) with poor quality hair fiber (**b**). Alternatively, inflammation might induce a truncated, rapid cycling through early anagen (or anagen of only brief duration) and telogen resulting in the production of limited hair fiber (**c**). Inflammation might also force hair follicles into a prolonged telogen state with no attempt to produce hair fiber (**d**). Possibly different intensities of inflammation, or chronicity of the disease, determine the nature of the hair follicle cycle perturbation. It is likely that more than one scenario occurs in an individual with AA

hair loss. The normal scalp hair follicle cycle involves a multiyear anagen growth phase followed by catagen regression and a brief telogen rest phase of just a few months. In AA this standard hair follicle cycle is altered, though there is some argument as to how exactly the affected hair follicles respond to inflammation. Three primary scenarios are possible (Fig. 15.2a–d). Anagen stage hair follicles may become inflamed but nevertheless they may maintain a dystrophic anagen state and continue to produce defective hair fiber or at least a keratinized material in some form (Fig. 15.2b). Alternatively, perhaps with greater intensity of inflammation, hair follicles may be forced into a truncated cycling state where attempts to return to an anagen growth phase are met with a renewed inflammatory cell attack pushing the hair follicle back into telogen (Fig. 15.2c). With persistent AA, hair follicles may be less inclined to attempt anagen growth and remain in a prolonged telogen state (Fig. 15.2d). While it is difficult to determine the exact hair follicle response in AA in humans [90], a mouse model of AA presents with different hair growth states depending on the stage of disease development. In the early acute phase, greater frequencies of hair follicles are found in a dystrophic anagen state. With the development of a chronic stable state of AA, most follicles remain in a telogen state. Thus the hair follicle response

to AA may depend on the intensity of inflammation and the duration of the disease.

15.5 Clinical Features

Alopecia areata is the symptomless loss of hair in small circumscribed patches (Fig. 15.3) which may either remain discrete or may expand into total loss over all the scalp (Fig. 15.4) and even body hairs including eyelashes (Fig. 15.5), eyebrows, and beard (Fig. 15.6). The affected scalp skin is usually without pathological findings and scarring does not occur. However, in some patients a mild erythema can be observed and some of them report slight itching in the balding lesions. But in general, the typical patient with AA notes the sudden appearance of circular patches of hair loss without any accompanying symptoms. Areas of activity in the lesion may be indicated by the presence of “exclamation mark” hairs (Fig. 15.7) which are usually 2–4 mm long and may have a dark expanded tip and a depigmented root, or by so-called point noirs (black dots), which are hairs that have broken off immediately after reaching the scalp surface. If the disease leads to complete scalp baldness, it is called alopecia areata totalis (AAT); if it involves additionally



Fig. 15.3 Patchy alopecia areata in a child

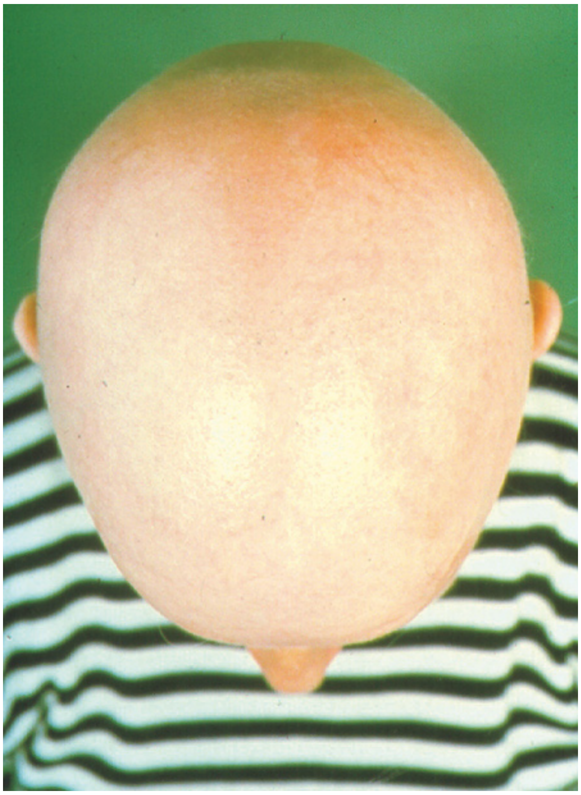


Fig. 15.4 Alopecia areata totalis

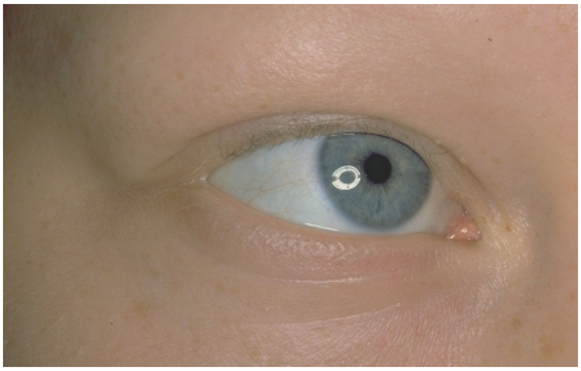


Fig. 15.5 Alopecia areata of eyelashes



Fig. 15.6 Alopecia areata barbae

body hair, it is called alopecia areata universalis (AAU). Alopecia areata of the neck is called the ophiasis type (Fig. 15.8). A very rare type is alopecia areata diffusa, resulting in a sudden diffuse hair loss.

The course of AA is unpredictable and typically characterized by phases of acute hair loss followed by spontaneous hair regrowth and waxing and waning of the lesions. However, in severe forms hair loss can persist for many years. Very often AA shows a mild clinical course with only a few small bald patches, and hair regrowth after some weeks or months. However, the severe forms are often chronic.

Hair color is commonly recorded as part of an AA-affected patient's history. There are several published cases of selective pigmented hair loss and white hair survival in AA-affected individuals, explaining how scalp can appear to become white overnight [28]. In addition, when an individual experiences hair regrowth, the hair is often white at first and only later does hair growth become pigmented. Much has been made of these observed phenomena in defining melanocytes as potential targets of inflammation in AA, although there are many more unreported examples of AA-affected individuals losing both pigmented and non-pigmented hair. However, at least in some individuals hair follicles producing pigmented hair are more susceptible to AA as compared to hair follicles producing unpigmented hair. This brings the possibility that gray-haired individuals may be less susceptible to the development of AA.

Nail involvement in AA is a variable feature. A significant number of AA patients may have some degree of nail dystrophy [27] (Fig. 15.9). Typical signs of nail involvement in AA are small pits and red-spotted lunulae, leukonychia punctata and vertical or longitudinal ridging may also occur. Sometimes all nails are affected. Severe forms of nail changes are sand-paper nails or a shiny twenty-nail dystrophy. In rare cases nails may fall off (onychomadesis). Nail involvement is usually associated with widespread AA. The nail changes associated with AA usually accompany the onset of hair loss, but may occasionally precede or follow the onset of alopecia by several months or years. The presence and severity of nail changes may indicate a more severe and recalcitrant disease. Marked nail dystrophy occurs more commonly in AAT, and AAU. The involvement of nails in the AA disease phenotype is also an indicator that melanocytes need not be the primary targets of inflammation.

The prognosis for AA is defined by the age at disease onset, duration, nails signs, the extent of hair loss,



Fig. 15.8 Alopecia areata "Ophiasis type" in a 16 year old boy

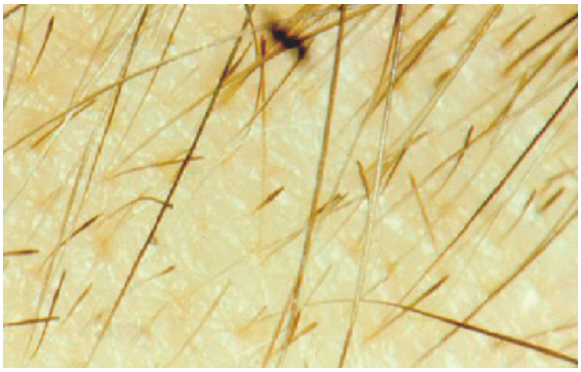


Fig. 15.7 Typical exclamation mark hairs found in the acute stage of alopecia areata



Fig. 15.9 Manifestion of alopecia areata on the nail plate

and the presence of atopic dermatitis. This means that a patient with AAU for many years, with a first episode of AA during childhood, associated nail changes, and atopic dermatitis has only a small chance of experiencing hair regrowth.

Except the nails, no other organs are affected by this disease. There are some publications which describe the association of AA with other autoimmune diseases such as vitiligo or type 1 diabetes mellitus. However, there is considerable debate about the statistical significance of these observations. In our view, only Hashimoto's thyroiditis tends to be more common in AA.

Taken together, AA is not life-threatening but it is psychologically and socially disturbing.

15.6 Pathology

Histopathological features of early AA include perifollicular and intrafollicular lymphocytic infiltrates involving only anagen hair follicles with subsequent miniaturization of these follicles. The lymphocytic infiltrate is located around the hair bulb with some lymphocytes invading the hair follicle (Fig. 15.10). In pronounced cases pigmentary incontinence is a typical feature. Occasionally plasma cells, mast cells, and eosinophils can also be seen. The T lymphocytes are predominantly of the T helper (CD4) subclass. Often all anagen hairs are affected and catagen hairs are seen. In later stages, often only empty fibrous sheaths can be seen with only limited inflammation. There are no signs of scarring.

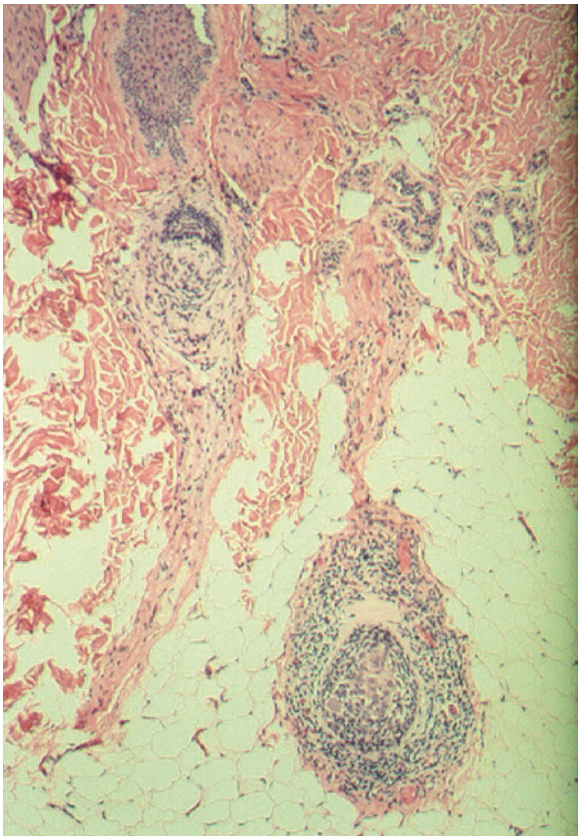


Fig. 15.10 Dense peribulbar lymphocytic infiltrated in alopecia areata (HE stain, ×100)

15.7 Differential Diagnosis

The clinical historry of abrupt onset of patchy hair loss, the lack of infection, point noirs, and exclamation mark hairs are all suggestive of the diagnosis of AA and in most cases the diagnosis of AA can be made clinically. There is no blood test to confirm or to rule out the diagnosis. In rare cases differential diagnosis such as chronic discoid lupus erythematosus, trichotillomania, lichen planopilaris, syphilis, traction alopecia, metastasis to the scalp, mycosis fungoides or alopecia mucinosa must be taken into consideration. Especially in AA of the diffuse type, it might be difficult to make the diagnosis. Then a scalp biopsy is indicated. Destruction of hair follicles or scarring usually does not occur in AA and therefore hair regrowth is possible at any time point of the disease, either spontaneously or due to a successful treatment. The process usually involves terminal hairs but can affect vellus hairs as well.

15.8 Treatment

Various methods to treat AA have been described, but for many of them only anecdotal reports exist and the alleged treatment success might be attributed to spontaneous remission. Because of the high rate of spontaneous hair regrowth in AA, the only treatments that can be regarded as evidence-based are those proven to be effective either after exclusion of spontaneous remission by treating every patient on one half of the scalp only or in a double-blind, placebo-controlled study including a very large number of patients. (For evidence levels, see Table 15.3.) Furthermore, studies evaluating a treatment for AA should preferably include patients with AAT, AAU, and extensive patchy AA (>25% scalp hair loss) persisting longer than 3 months, because these patients have a worse prognosis than patients with limited patchy AA. These patients are also the ones who are

Table 15.3 Quality of evidence and strength of recommendation as given by the British Association of Dermatologists in 2003 [47]. This guideline does not consider publications after 2003

Therapy	Quality of evidence[a]	Strength of recommendation[b]
Topical corticosteroids	III Evidence based data on clobetasol under occlusion and clobetasol foam were published in 2006	C Evidence data on clobetasol under occlusion and clobetasol foam were published in 2006
Intralesional corticosteroids	III	B
Systemic corticosteroids	III	C
PUVA	III	C
DCP / SADBE	II-ii	B

[a] Evidence levels/Quality of evidence (according to the guidelines of the British Association of Dermatologists 2003):

I. Evidence obtained from at least one properly designed, randomized controlled trial

II-i. Evidence obtained from well-designed controlled trials without randomization

II-ii. Evidence obtained from well-designed cohort or case-control analytical studies, preferably from more than one centre or research group

II-iii. Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence

III. Opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees

IV. Evidence inadequate due to problems of methodology (e.g. sample size, or length of comprehensiveness of follow-up or conflicts of evidence.

[b] Strength of recommendations

A There is good evidence to support the use of the procedure

B There is fair evidence to support the use of the procedure

C There is poor evidence to support the use of the procedure

D There is fair evidence to support the rejection of the use of the procedure

E There is good evidence to support the rejection of the use of the procedure

most in need of an effective treatment. Any treatment has to be suitable for long-term therapy, because AA is a disease that can persist for many years or even life. Hence, all therapeutic approaches showing severe side-effects are inappropriate for AA in the long run.

15.8.1 Immunosuppressive Treatments

15.8.1.1 Corticosteroids

Topical, intralesional, and systemic corticosteroids have been used for the treatment of AA with different rates of success and side-effects.

15.8.1.2 Topical Corticosteroids

Topical treatment of AA with corticosteroid creams, ointments or lotions are frequently used for the treatment of AA. However, only two placebo-controlled studies fulfilling the criteria of evidence-based medicine reported a treatment response, both using clobetasol propionate 0.05% [85, 86]. In 9% of patients with patchy AA treated with a clobetasol propionate 0.05% foam hair regrowth >75% was observed; 20% of patients experienced hair regrowth of >50% [85]. However, patients with AAT or AAU did not respond to treatment with the clobetasol foam. A more effective treatment for patients with AAT or AAU is the application of clobetasol propionate 0.05% ointment under occlusion. Tosti

reported a treatment success of 17.8% in patients with AAT and AAU when clobetasol propionate 0.05% ointment was applied under occlusion for 6 nights a week for 6 months [86]. Therefore, topical corticosteroids can only be recommended when clobetasol propionate 0.05% is used and even then it will only be effective in some patients with severe AA when occlusive application is used or exclusively in single patients with patchy AA when clobetasol foam is applied.

15.8.1.3 Intralesional Corticosteroids

Intralesional injections of corticosteroid crystal suspensions, primarily triamcinolone acetonide, have been used for the treatment of AA for more than 40 years (reviewed in [21, 22]). Several studies reported hair regrowth at the site of injection in the majority of cases (Table 15.4) (reviewed in [21, 22]). Most of these studies tried to exclude spontaneous hair regrowth by comparing the injected sites of the scalp with uninjected areas, especially in AAT. However, in practice it is impossible to treat the whole scalp by intralesional injections of corticosteroids and so this treatment is only indicated in patchy AA with longstanding bald areas. Apart from the sometimes painful procedure of injection, permanent skin atrophy can occur after injection. Taken together, intralesional injection of corticosteroids is a reasonable treatment in selected cases of longstanding small patches of AA.

15.8.1.4 Systemic Corticosteroids

Alopecia areata has been treated with systemic corticosteroids since 1952 (reviewed in [21, 22]). Whereas initially corticosteroids were taken orally daily or every other day for several months, this approach of continuous corticosteroids application is now obsolete. The doses that are required to maintain hair regrowth in AA are between 30 and 150 mg daily, giving rise to unacceptable side-effects such as hypertension, diabetes, immunosuppression, osteoporosis, and susceptibility to thrombosis.

Since 1975 several authors have performed pulsed administration of corticosteroids in single doses, given once monthly in order to reduce the side-effects of corticosteroids to an acceptable level. Major side-effects have not been observed in pulsed administration of corticosteroids to AA patients; side-effects that occurred were striae, nausea, flush, headache, polymenorrhea, fatigue, palpitations, dyspnea, and giddiness. The way the pulse therapy was performed varied between the studies. Some authors applied the corticosteroids intravenously, using either 500 mg methylprednisolone i.v. for 3 days or 8 mg methylprednisolone/kg body weight on 3 consecutive days at 4-week intervals for at least three courses. Other groups applied the corticosteroids orally with a median dose of 5 mg prednisolone/kg body weight once monthly for 3–9 months or 80 mg predonine for 3 days consecutively once every 3 months (reviewed in [21, 22]) [41, 74]. Some authors observed cosmetically acceptable hair regrowth in patients treated by pulsed administration of corticosteroids, but their studies were not controlled and the majority of patients responding to treatment had patchy AA, which usually shows a high rate of spontaneous remission. Hence, the observed hair regrowth after treatment may also be due to spontaneous remission. Moreover, other studies reported a treatment failure after corticosteroid pulse therapy, especially in patients suffering from AAT and AAU (reviewed in [21, 22]) [74]. Therefore, controlled studies are urgently required to prove the efficacy and long-term value of this treatment. In particular, the efficacy in interrupting acute phases of rapid hair loss by pulsed administration of oral corticosteroids should be investigated.

Table 15.4 Clinical studies assessing treatment of AA with intralesional steroids

Reference	Controlled study	Number of patients	Cosmetically acceptable hair regrowth at injection site (%)
Kalkoff and Macher 1958 [40]	No	15	100
Orentreich et al. 1960 [65]	No	20	90
Porter and Burton 1971 [69]	No	11	55
Fülöp and Vajda 1971 [24]	No	66	74
Abell and Munro 1973 [1]	No	84	45
Frentz 1977 [20]	Yes	6	33

15.8.2 Psoralen UV A Therapy

Several studies have been performed on the treatment of AA with psoralen UV A (PUVA) therapy using either oral application of 8-methoxypsoralen (8-MOP) with ultraviolet A radiation (UVA) of the scalp or the whole body, or topical application of 8-MOP and UVA radiation on the scalp, including one study with topical application of psoralen via the PUVA-turban (reviewed in [21, 22]). Some investigations seemed to show good results (reviewed in [21, 22]), but there were no controls in any of the studies. Moreover, there was a high number of AA recurrences in most of the studies (between 30% and 50% of successfully treated patients) after initial hair regrowth, which strongly decreases the efficacy of PUVA treatment for AA (reviewed in [21, 22]). This high number of relapses is most likely due to the fact that regrown hair inhibits the UVA light from reaching the skin. Technical improvements, such as a comb emitting UVA light, have been tried, but so far no results have been reported. Unfortunately, continuous hair regrowth after the initial response has to be actively maintained for several years in most cases of AA, bearing an increased risk of skin malignancies after long-term PUVA therapy.

15.8.2.1 The 308-nm Excimer Laser

Using the immunosuppressive properties of the 308-nm Excimer laser, two small within-patient controlled studies have been performed recently that demonstrated a successful treatment of patchy AA. Treatment was performed for about 3 months in 24–27 sessions using 0.2–7.6 J/cm² resulting in a cumulative dose varying between 3.9 and 52.6 J/cm². However, the 308-nm Excimer laser was not able to treat AAT or AAU in these studies [33, 94]. Therefore larger controlled studies are needed to assess the efficacy, safety, and the long-term results of AA treatment with the 308-nm Excimer laser and to evaluate whether this might be a therapeutic option for the future.

15.8.3 Immunomodulatory Treatments

15.8.3.1 Diphenylcyclopropenone and Squaric Acid Dibutylester

Alopecia areata has been treated with contact sensitizers for more than 25 years. Dinitrochlorobenzene (DNCB) was the first sensitizer that was used for the treatment of AA, but because it has been shown to be mutagenic in the Ames test, it can no longer be used [34, 35]. Today diphenylcyclopropenone (DCP) or squaric acid dibutylester (SADBE), which are not mutagenic in the Ames test, are widely used in European states and in Canada.

15.8.3.2 Treatment

Treatment with contact sensitizers is preceded by sensitization of the patient with 2% DCP solution on a small area of the scalp. Two weeks later, treatment is initiated by application of a 0.001% DCP solution, followed by weekly application of increasing concentrations of DCP until a mild eczematous reaction is obtained. In this way, an appropriate eliciting concentration of DCP for each patient is identified. Concentrations frequently used are 0.001%, 0.005%, 0.01%, 0.05%, 0.1%, 0.5%, 1% or 1.5% but some patients may need lower concentrations such as 0.00001% or the highest concentration of 2%. This concentration has to be applied once a week to induce a mild eczematous reaction that is characterized by itching and erythema, without blistering or oozing. During the course of treatment the patient's reaction to this initially identified concentration may change so that a higher or lower concentration has to be used. Some patients develop tolerance against DCP, so that they do not show an allergic reaction even after application of 2% DCP. In these patients SADBE is used. It is applied in the same way and shows a similar rate of response. DCP or SADBE is dissolved in acetone and should be applied with a thin cotton applicator, using only a very small amount of DCP or SADBE, so that the solution never drops off the cotton applicator.

Initial hair regrowth is usually visible after 8–12 weeks. Treatment has to be continued once weekly until complete hair regrowth is obtained. Treatment intervals are then decreased and eventually treatment may be discontinued. However, if a relapse occurs after discontinuation of therapy, treatment can be restarted immediately to stop further progression of AA and induce renewed hair growth. Treatment should initially always be applied on one half of the scalp and the other side left untreated to exclude a spontaneous hair regrowth coincidental to treatment initiation. Treatment is continued on both sides only after the treated side has shown a response in the form of better hair growth on the treated side (Fig. 15.11).

15.8.3.3 Side-Effects

A mild eczematous reaction and enlargement of retroauricular lymph nodes are desired reactions and inherent to treatment. They are usually well tolerated if the patients are informed that these reactions are desirable for the therapeutic effect. In order to mitigate itching, an oral antihistamine can be used. Undesired side-effects



Fig. 15.11a–c Treatment of AA with a contact sensitizer: unilateral contact dermatitis after application of a contact sensitizer on the left side of the scalp with erythema but no vesicular reaction (**a**); unilateral hair growth on the treated side (**b**); complete hair growth after treatment of both sides (**c**) (from [34])

are noted in 2%–5% of patients (reviewed in [21, 22]). Vesicular or bullous reactions sometimes occur at the beginning of treatment before the individual appropriate concentration has been determined. The patients have to be advised to wash off the contact sensitizer immediately if bullous reactions occur and apply a topical corticosteroid. Treatment has to be interrupted for 2 weeks and can then be continued with one-tenth of the last concentration of the contact sensitizer.

Dissemination of allergic contact dermatitis, urticarial or erythema multiforme-like reactions may occur but can be successfully treated with topical corticosteroids. Pigmentary disturbances such as postinflammatory hyperpigmentation with spotty hypopigmentation ("dyschromia in confetti") have been observed, especially in patients with dark skin, but resolved within 1 year after discontinuation of treatment in most cases. Apart from these acute and subacute side-effects, no long-term side-effects have been reported after 21 years of DCP (24 years of SADBE) treatment worldwide of about 10,000 patients, including children. However, it should be borne in mind that DCP and SADBE are not approved therapeutic substances.

15.8.3.4 Studies

More than 25 studies have been performed to test the efficacy of AA treatment with a contact sensitizer. The most significant controlled studies are listed in Table 15.5. The majority of contact sensitizer treatment studies were controlled, most of them using an untreated side of the scalp as a control. When comparing the rates of response obtained in various therapeutic modalities, one should bear in mind that spontaneous regrowth is excluded in these controlled, within-patient studies but not in the uncontrolled studies proving the efficacy of systemic corticosteroids or PUVA treatment. The response rate of treatment with a contact sensitizer varies between 29% and 78% resulting in a median response rate of all studies of 49%, rendering contact sensitizers an effective therapeutic tool for AA.

15.8.3.5 Mode of Action

The mode of action of the treatment with contact sensitizers remains poorly understood. It has been shown that treatment with a contact sensitizer changes the composition and localization of the perifollicular infiltrate. After treatment with a contact sensitizer the mRNA-expression of interferon gamma (IFN-γ) is reduced while the expression of interleukin-10 (IL-10) is increased (reviewed in [21, 22]). Whether this is due to a Th1-Th2 shift or the introduction of regulatory T-cells with a type-2 cytokine profile is the object of current investigations. Recent studies demonstrated that treatment with a contact sensitizer induces apoptosis in perifollicular T-cells [37].

Table 15.5 Treatment of AA with contact sensitizers, controlled studies including patients with severe, longstanding AA. (*DCP* Diphenylcyclopropenone, *SADBE* squaric acid dibutylester, *ULT* unilateral treatment, untreated side serves as control)

Reference	Contact Sensitizer	Clinical form of AA (number of patients)			Controlled study	Number of patients	Cosmetically acceptable hair regrowth (%)
		Patchy AA	AA totalis	AA universalis			
Happle et al. 1983 [35]	DCP	5	22	0	Yes (ULT)	27	68
Happle et al. 1984 [36]	DCP	8	37	0	Yes (ULT)	45	58
Ochsendorf et al. 1988 [64]	DCP	18	8	1	Yes (ULT)	27	37
Macdonald Hull and Norris 1988 [45]	DCP	8	20	0	Yes (ULT)	28	29
Monk 1989 [61]	DCP	0	14		Yes (ULT)	14	43
Steen van der et al. 1991 [79]	DCP	78	32	29	Yes (ULT)	139	50.4
Macdonald Hull et al. 1991*b* [46]	DCP	4	8	0	Yes (ULT)	12 children	33
Macdonald Hull et al. 1991*a* [44]	DCP	33	45	0	Yes (ULT)	78	55
Hoting et Boehm, 1992 [39]	DCP	11	20	14	Yes (ULT)	45	51
Gordon et al. 1996 [32]	DCP	12	36	0	Yes (ULT)	48	38
Schuttelaar et al. 1996 [73]	DCP	10	16	0	Yes (ULT)	26 children	32
Weise et al. 1996 [89]	DCP	43	22	40	Yes (ULT)	105	48
Cotellessa et al. 2001 [15]	DCP	14	42	0	Yes (ULT)	56	48
Wiseman et al. 2001 [91]	DCP	113	35	0	Yes (ULT)	148	77.9
Happle et al. 1980 [34]	SADBE	26	27	0	Yes (ULT)	53	70
Case et al. 1984 [10]	SADBE	11	10		Yes (ULT)	21	52
Caserio 1987 [11]	SADBE	2	5	7	Yes (ULT)	14	29
Micali et al. 1996 [58]	SADBE	129	8	0	Yes (ULT)	137	64

Furthermore, immunohistochemical studies have shown that treatment with a contact sensitizer reduces the aberrant expression of MHC class I and MHC class II molecules on the lower hair follicle epithelium (reviewed in [21, 22]). From these data it can be concluded that treatment with a contact sensitizer may restore the immune privilege of the lower hair follicle epithelium.

15.8.4 Other Treatments

15.8.4.1 Irritant Contact Dermatitis – Anthralin

Even though treatment of AA with an irritant contact dermatitis is performed by many dermatologists, it has never been shown to be successful in a controlled study. In a half-side controlled study, using 0.1% anthralin that resulted in a mild irritant contact dermatitis, no difference between the treated and untreated sides was observed (reviewed in [21, 22]).

15.8.4.2 Minoxidil

Because of its stimulating effect on hair growth, which is proven in androgenetic alopecia, various authors have attempted to used topical minoxidil solution in AA as well. Unfortunately none of the studies that claim successful treatment of AA with minoxidil fulfilled the criteria of evidence-based treatment of AA (reviewed in [21, 22]). Six other placebo-controlled studies performed by various groups did not show a statistically significant difference between the hair growth of patients treated with the placebo or with minoxidil. In three of these studies cosmetically acceptable hair regrowth was not even observed in a single patient (reviewed in [21, 22]). In summary, minoxidil is not useful in the treatment of AA.

15.8.4.3 Biologics

Based on the knowledge that AA is a T-cell-mediated autoimmune disease, various biologicals that have been proven to be effective in psoriasis therapy have also been tried in the treatment of AA. But neither tumor necrosis factor alpha (TNF-α) inhibitors such as etanercept or infliximab nor the LFA-1 inhibitor efalizumab was effective in treating AA [70]. It seems rather that TNF-α inhibitors worsen the course of the disease [18]. Hence it remains to be explored whether future biologicals could be useful in the treatment of AA.

Summary for the Clinician

Alopecia areata (AA) is regarded as a T-cell-mediated autoimmune disease that is directed against an undefined autoantigen of the hair follicle. There is a genetic predisposition to develop AA, and environmental triggers have not yet been identified. The diagnosis can be established by characteristic clinical features of AA including its severe forms AA totalis and universalis as well as ophiasis. The presence of exclamation mark hairs, point noirs, nail changes, and the report of former episodes with spontaneous remission may help confirm the diagnosis. In some cases a histopathological examination may be necessary, whereas other laboratory investigations are usually not required. Because of the high rate of spontaneous remission, the efficacy of a rational treatment for AA has to be proven in controlled

Table 15.6 Treatment suggestions for different types of AA

Type of AA	Treatment suggestions	
Short-standing, limited patchy AA	No treatment *or*	
	Topical corticosteroids:	Clobetasol-foam twice daily
Longstanding patchy AA	Topical corticosteroids	Clobetasol-foam twice daily
		Clobetasol-ointment occlusive overnight
	Intralesional corticosteroids	
	Topical immunotherapy with diphencyprone or SADBE	
AAT / AAU	Topical immunotherapy with diphencyprone or SADBE	
	Clobetasol-ointment occlusive overnight	

studies. An ideal treatment should be highly effective but associated with only minor side-effects. According to the rules of evidence-based medicine, treatment with the contact sensitizers diphencyprone (DCP) or squaric acid dibutylester (SADBE) is at present the most effective for severe AA, e.g., AA totalis, universalis or patchy AA with more than 30% hair loss. The application of clobetasol propionate 0.05% under occlusion might be a therapeutic option for a minority of patients with severe AA. For treatment of limited patchy AA, intralesional corticosteroids are proven to be effective, and treatment with the new clobetasol 0.05% foam might be useful in isolated cases (Table 15.6). Even though oral pulse therapy with corticosteroids and PUVA therapy are widely used to treat severe AA, there are no well-designed controlled studies proving their efficacy.

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Chapter 16

Hypertrichosis

Francisco M. Camacho-Martínez

16

Synonyms
polytrichosis

Key Features

- Hypertrichosis is the growth of hair of an excessive amount and thickness on any part of the body.
- The term is frequently confused with hirsutism, which should only be applied to women with an excessive development of hair with a male pattern distribution.
- Hypertrichosis is classified in generalized, localized, or symptomatic. All types can also be classified according to the age of onset as congenital or acquired.
- Generalized, symptomatic, and localized forms of congenital hypertrichosis are present in several genodermatoses. Localized forms may also appear in relation to underlying hamartomas.
- Generalized acquired hypertrichosis may be a paraneoplastic syndrome, such as acquired hypertrichosis lanuginosa; it may be localized, the result of association with abnormalities of the fat, muscle, bone or of the underlying hemodynamic system; or it may be related to multiple direct cutaneous traumas.
- The most frequent acquired symptomatic forms of hypertrichosis are iatrogenic.
- Long-term removal of unwanted hair is the objective.

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16.1 Introduction

The presence of undesired hair growth can be very troublesome to many people, not only women. Currently, this disease needs a clear dermatologic diagnosis with the purpose of detecting underlying systemic or dermatological diseases. Equally important is the treatment of these unwanted hairs with topical procedures including laser therapy [17, 70].

16.2 Clinical Features

The excessive growth of hair may be generalized or localized, and may have a wide range of etiologies from repeated trauma to genodermatoses to underlying hamartomas [70, 94] (Table 16.1).

16.3 Generalized Hypertrichosis

This is the presence of fetal-type vellus hair, or normal hair, on the entire skin surface, and even the transformation of terminal hair into lanugo hair at a certain time of life. Depending on whether one or the other is present, there are three options, analyzed below.

16.3.1 Congenital Hypertrichosis Lanuginosa

16.3.1.1 Introduction

This is a rare autosomal-dominant disease although there are also reports of X-linked dominant and autosomal-recessive inheritance patterns [94] (OMIN: 145700, 307150). One-third of the described cases are sporadic.

16.3.1.2 History

The first description of the syndrome appeared in the German literature, specifically in the work of R. Virchow [53], in 1870; there are also many cases in history which should be considered as such. Examples include the family of Pedro González, who was born in 1556 and lived at the court of Henry II of France and who had three affected children; and the Shwe-Maong family, from Barma (India), who were discovered in 1826 by the Governor-General of India, John Crawford, when he visited the court of King Ava, and Shwe-Maong was there as a buffoon. He married and had four daughters, and one of them, Maphoon, also had hypertrichosis lanuginosa. Maphoon married and had two children who at first appeared normal, but one of them, at the age of 14 months, showed a significant hairy tuft over the left ear [11].

16.3.1.3 Clinical Features

The principal feature is that the fetal vellus hair is not replaced by normal hair and continues to grow until reaching a length of 10 cm on the entire body surface, except for the palms, the soles, the dorsal surface of the distal phalanges, the prepuce, and the glands of penis, which overall effect gives the face a “dog” or “monkey” aspect. The lanugo hair, of a blond, silvery, or chestnut color and a woolly texture, is much more evident at the level of the vertebral column and the lumbosacral area, the ear, and the preauricular and sacral areas [53]. These children are sometimes born normal, or, as in the Beighton’s case, with coarse black hair on the head and the eyebrows [9], with the hypertrichosis starting to develop in early infancy, between the ages of 4 and 7. As time goes by, there may be a reduction of the lanugo on the trunk and the extremities, but this does not occur on the face, which requires treatment.

In the majority of patients this only causes an esthetical problem; however, there have been cases in which there has been an association with hypo- or anodontia, and even with early dentition [9], defects of the ear, glaucoma [53], pylorum stenosis, skeletal abnormalities and, exceptionally, physical and mental retardation, and photophobia [17].

16.3.2 Acquired Hypertrichosis Lanuginosa

16.3.2.1 Introduction

This is considered to be a “*paraneoplastic dermatosis*,” as it accompanies carcinomas of the lung, colon, bronchi, rectum, prostate, liver, pancreas, breast, ovaries, uterus, pancreas, bladder, gallbladder, cervix, lymphomas, and leukemia [48]. Hypertrichosis lanuginosa is an indicator of a poor prognosis.

16.3.2.2 History

The first description of the syndrome was made by Turner in 1865, in a woman with breast carcinoma, and then there were no further publications until 1951. From then until 1993, 41 cases were published, with the male:female ratio being 2.4:1, the average age being predominantly between 40 and 70 years [49], and lung carcinoma being the most common in men and colorectal carcinoma being the most common in women [63]. Association with carcinoma of the cervix was recently described [82].

Occasionally, acquired hypertrichosis lanuginosa may precede the neoplasm by several months or years [72], and in other situations there was no evidence of malignant pathology during life, but this was discovered on autopsy. It has been described as accompanying a disseminated melanoma with diffuse cutaneous melanosis [8]. It may be associated with other paraneoplastic dermatoses, such as acanthosis nigricans, acquired ichthyosis, *punctate palmoplantar keratoderma*, polymyositis [78], the sign of Leser-Trélat, and florid cutaneous papillomatosis [97]; it has also been described in association with scleroderma, amenorrhea, galactorrhea, thrombocytopenia, and alopecia of the axillary and the pubic areas.

Table 16.1 Classification of hypertrichosis

I. Generalized hypertrichosis	1. Congenital hypertrichosis lanuginosa
	2. Acquired hypertrichosis lanuginosa
	3. Universal hypertrichosis
	4. Pubertal hypertrichosis
II. Localized hypertrichosis	1. Congenital localized hypertrichosis
	2. Acquired localized hypertrichosis
III. Symptomatic hypertrichosis	1. Genodermatosis
	2. General and dermatological acquired diseases
	3. Iatrogenic hypertrichosis

16.3.2.3 Clinical Features

The “fetal lanugo” hair sprouts all over in a short time, although in mild forms this may be located particularly on the face, where it grows rapidly, up to 2–3 cm a week, reaching lengths of up to 15 cm, which leads to a “simian” face. The hair on the head, the beard hair, and the pubic hair are not usually modified, but, with the exception of the palms, the soles, prepucio and the glands of the penis, the rest of the body surface shows a large, white-yellowish lanugo. This may even appear on the previously alopecic scalp [78].

In some patients there has been glossitis of the distal two-thirds of the tongue, characterized by glossodynia, burning pain, hypertrophy of the papillae, pronounced folds, taste disorders with a salty taste, angiomatous stains on the tongue, pigmented maculae on the oral mucosa, and also sensation changes of the olfactory nerves [48].

16.3.2.4 Pathogenesis

Herzberg [48] has indicated that there are two possibilities: (1) synchronization of the lanugo anagen and (2) retrograde morphogenesis of terminal hair. In the former, anagen and telogen are different for the different types of hairs, including lanugo, depending on its location, but in this type of hypertrichosis, hair continues to grow without any diurnal or nocturnal rest periods, until the patient dies or the tumor is eliminated. In the latter, growth of the lanugo hair is limited to those areas of the body where it is normally found; that is to say, on the nose, the forehead, the cheeks, and the ear, with the only difference being the texture, as the lanugo is now much thicker.

In any case, whenever an acquired hypertrichosis is diagnosed, a possible underlying malignancy must be investigated, as, if this is found and eliminated, the hypertrichosis may disappear.



Fig. 16.1 Universal hypertrichosis, showed a normal hair distribution pattern, but with a manifest increase in hair, both in thickness and in length, on the back of a man with androgenetic alopecia degree VII of Hamilton

16.3.3 Universal Hypertrichosis

16.3.3.1 Introduction and History

This is an autosomal-dominant disease that has a variable expression. It must clearly be separated from dominant sex-bound hypertrichosis, of which there is only one family, described in 1984 by Macías Flores et al. [60], in which the males showed a significant symmetrical hypertrichosis and the females showed asymmetrical plaques.

16

16.3.3.2 Clinical Features

The individuals who present universal hypertrichosis show a normal hair distribution pattern, but with a manifest increase in hair, both in thickness and in length, in the areas which are normally hairy, such as the thorax and the back in men (Fig. 16.1), with the palms and the soles always being respected. Some authors do not consider this situation to be pathological, but rather exaggerated normal hairiness. Although this opinion may be considered correct, it should not be forgotten that those who have this type of hypertrichosis usually have serious psychological problems.

16.3.4 Prepubertal Hypertrichosis

Prepubertal hypertrichosis is seen in otherwise healthy infants and children. The distribution is generalized and becomes more obvious during childhood. There is involvement of the face, proximal extremities and back; hairs on the latter location assume an inverted fir-tree pattern [17].

16.4 Localized Hypertrichosis

16.4.1 Congenital Localized Hypertrichosis

Hamartomas, including those with a delayed clinical presentation, and congenital abnormalities characterized by a circumscripted hypertrichosis of a specific anatomic site are included in this category. We shall tentatively follow the classification of Table 16.2 [21].

16.4.1.1 Melanocytic Nevus

16.4.1.1.1 Congenital Melanocytic Nevi and Plexiform Neurofibroma

16.4.1.1.1.1 Introduction

These nevi are separated from the rest of the nevocytic (pigmentocellular) nevi, which are discussed in the next section, because of their undisputed greater tendency towards malignancy, especially in the giant forms which are located in the medial line of the back [21].

Table 16.2 Localized congenital hypertrichosis

1. Melanocytic nevi	1.1 Congenital melanocytic hairy nevi	
	1.2. Acquired melanocytic nevi	
2. Becker's nevus		
3. Nevoid hypertrichosis	3.1. Primary nevoid hypertrichosis	a. Hairy elbow syndrome
		b. Hypertrichosis of the auricle („hairy pinna")
		c. Eyebrow hypertrichosis
		d. Hairy polythelia
		e. Anterior cervical hypertrichosis
		f. Primary multifocal localized hypertrichosis
	3.2. Secondary nevoid hypertrichosis:	
4. Spinal dysraphism		



Fig. 16.2 Congenital melanocytic nevi in the form of a "shirt's arm"

16.4.1.1.1.2 Clinical Features

These appear with capricious shapes and sizes, in metameric or systematized topographies. In the latter case they are called according to "the piece of clothing which they simulate"; for example, a mask, a shirt, a shirt's arm (Fig. 16.2), shorts, a cerebriform helmet, a bathing suit. Hypertrichosis is seen in 95% of cases and although the increased hair growth may be noted at birth, it often becomes more prominent during infancy or early childhood [17]. A particularly dense growth of terminal hairs may accompany scalp nevi [17].

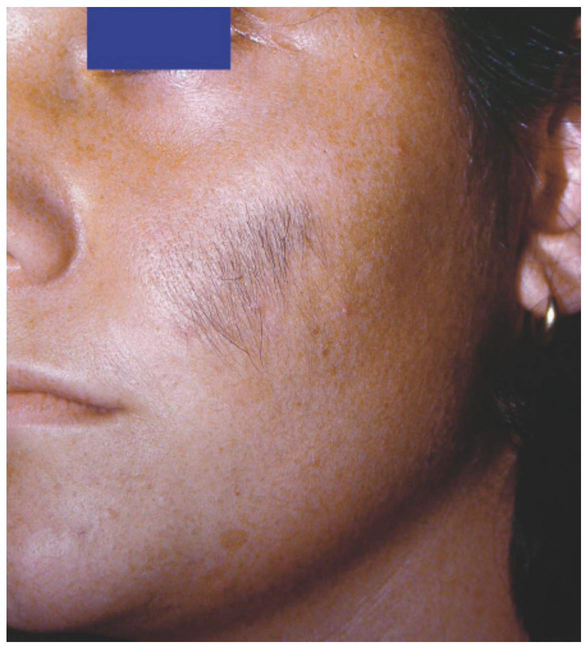


Fig. 16.3 Patient with neurofibromatosis of von Recklinghausen with typical hepatic spots on her face and plexiform neurofibroma on her left cheek with hypertrichosis

These nevi may be associated with ocular disorders, neurofibromatosis, bone malformations and leptomeningeal participation (*neurocutaneous melanoblastosis*), with hydrocephaly, intracranial hypertension, epilepsy, paraplegia, oligophrenia, etc. [17]. Nevertheless, plexiform neurofibromas can also have associate hyperpigmentation and hypertrichosis [17] (Fig. 16.3).

16.4.1.1.1.3 Pathology

The melanocytic proliferation involves the dermis and/or the hypodermis, and determines junctional activity, which is very high at the excretory ducts of the eccrine sweat glands and the outer root sheath under the isthmus, and at the level of the matrix cells of the sebaceous glands. There is perineural infiltration of the erector muscles, and subendothelial accumulations in the lymphatics and the blood vessels. There is an abundance of nerve fibers.

16.4.1.1.1.4 Evolution

Malignancy, when this occurs, develops from the melanocytes of the dermoepidermic limit, and less often from the deep and hypodermic dermal nevic cells (neuroids). At present it is considered that 13% of melanomas are associated with a nevus, and 0.6% of congenital nevi end up as a melanoma, which is why even those who do not favor systematic intervention for nevi agree that there should be periodic controls.

16.4.1.1.1.5 Treatment

The risk index of congenital nevi depends on their size: while large nevi have a risk of 6.3%, the risk associated with small ones varies between 2.5% and 8%. When considering just small nevi, the best risk indicator for these is their number [56].



Fig. 16.4 Nevus of Becker on the left scapular region with slight hyperpigmentation and severe hypertrichosis

16.4.1.1.2 Acquired Melanocytic Nevi

These are circumscribed neoplasias of the cutaneous melanocytic system. They are very frequent, to such a point that all individuals in the fourth decade of their lives have approximately 25 of them [14].

Nowadays there is no doubt that ultraviolet radiation is a risk factor for the development of nevi and melanomas. It has been shown that on the exposed areas of people with atypical nevi and melanomas, and even in controls, there are four times more nevi than in the protected areas such as the buttocks, and, moreover, the number is greater in the former. If patients present atypical nevi, the difference in the number of nevi is even greater. These data affirm the idea that sunlight plays an important role in the development of nevi, and may explain why a large number of nevi may be a “marker” for a melanoma [5].

16.4.1.1.2.1 Treatment

At present, apart from surgical treatment, pigmentary lesions benefit from Q-switched ruby laser (selective photothermolysis), although they are not totally eliminated.

16.4.1.2 Becker’s Nevus

16.4.1.2.1 Introduction and History

Described in 1949 by Becker, this is the presence of a hyperpigmented and hypertrichosis macula, with irregular borders, which is preferably located on the thorax, the shoulder and the scapular region (Fig. 16.4), covering the corresponding upper extremity [73].

16.4.1.2.2 Clinical Features

This is a hamartoma that usually arises in the first decade of life. Hypertrichosis usually appears in the second decade, and it is possible to observe severe hyperpigmentation and dense growth of hairs.

Approximately 80%–85% of the cases are male. When it is familiar, which is exceptional, it suggests an autosomal-dominant inheritance with incomplete penetration and variable expression. This incomplete penetration would be explained by *“paradominant”* inheritance [43]. This can be seen in other locations such as the abdomen, gluteus, and lower extremities, and as an exception may be bilateral (Fig. 16.5).



Fig. 16.5 Bilateral thoracic nevus of Becker that reaches the upper extremities

16.4.1.2.3 Associations

Becker's nevus may be associated with other internal abnormalities, is more common in women, and includes breast hypoplasia of the affected area [22], which sometimes reaches the upper extremities and the pectoral muscle [34]; there may also be asymmetry of the extremities, and spina bifida. It has also been described in association with hamartomas of the smooth erector muscles, connective tissue nevus, neurofibromas, abnormalities of the underlying fatty and bone tissue, morphea, and accessory scrotum. Rarely, there may be an association with genitourinary tract abnormalities (SNUB syndrome: supernumerary nipples, uropathies, Becker's nevus) [35].

16.4.1.2.4 Pathology

Becker's nevus shows a slight hyperkeratosis, acanthosis, and elongation of the interpapillary crests. There is an increased number of epidermal melanocytes, melanin is more abundant in the basal layer cells, and there are many melanophages in the superficial dermis. It does not present with nevic thecae. The hair follicles are normal, although they are increased in number. Electron microscopy shows that there are giant melanosomes in both melanocytes and keratinocytes of the nevus.

16.4.1.2.5 Etiology

Unknown; nevertheless, the greater incidence in men, commencement in puberty, and the association with hypertrichosis suggest a role for androgens. It has been shown that there is an increase in the number of androgenic receptors in the nevus [43], which accounts for hypoplasia of the ipsilateral breast and arm in women [22].

16.4.1.2.6 Evolution

The nevus tends to remain constant throughout life. Occasionally the hue of the coloration tends to decrease [43]. Various cases of melanomas in association with Becker's nevi have been described [31]; however, this association is not significant because as has already been noted, aside from epidemiological reasons, these nevi have no relation with the epidermal melanocytes, but only with the pigmentation [80].

16.4.1.2.7 Differential Diagnosis

A differential diagnosis of melanocytic nevi could be made, although, as already noted, the dermatopathology will allow a distinction to be made. Alternatively the differential could be acquired localized hypertrichosis, especially those secondary to traumatisms. Other alternatives are smooth muscle hamartomas, and localized or circumscribed hairy dysembryoplasias, usually located on the palms and the soles [19].

16.4.1.2.8 Treatment

It should be noted that, due to their extent and their usually benign character, surgical removal is not recommended. Some patients prefer epilation by electrolysis or by laser [17].

16.4.1.3 Nevoid Hypertrichosis

These are uncommon congenital alterations characterized by the growth of terminal hair in a circumscript area without any other systemic association [17]. When it is associated with an underlying defect, it is considered to be a "secondary nevoid hypertrichosis" [30].

16.4.1.3.1 Primary Nevoid Hypertrichosis

We shall consider the six entities listed below.



Fig. 16.6 Girl aged 7 years old with a hairy elbow that spread to the arm and forearm

16.4.1.3.1.1 Hypertrichosis Cubiti (Hairy Elbow Syndrome)

Described by Beighton in 1970 [9], this is a congenital malformation characterized by the presence of hypertrichosis symmetrically at birth, or which develops during the infancy around the elbows, extending from midhumerus to midforearm [3, 17, 94]. Initially the hairs tend to be fine, like the rest of the hairs that tend to be present in these patients, but later on, at approximately aged 5, these become long and woolly (Fig. 16.6), tending to disappear as of adolescence. It is not associated with endocrinological disorders, or with systemic disorders, although it has been associated with short stature (the most frequent association) [79], brachydactyly, short nails, short nose, antimongoloid slant of the eyes, ptosis and an asymmetrical face, diabetes mellitus, limb abnormalities and developmental disorders; nevertheless, in our observations the psychomotor and weight height development was adequate for the age [38]. There are no dermatopathological findings of interest, as the only biopsy yet taken showed that 90% of the follicles were in anagen; however, this high percentage of anagen hairs on the elbow might explain why the hairs were longer than usual. The genetic transmission mode of the familiar cases is unknown [3], because although this is considered to be autosomal dominant, a recessive pattern cannot be excluded [28].

In McKusick's catalogue of genetic diseases, this is number 139,600. Sometimes one can see association with hypertrichosis of the lumbosacral area, without evidence of spina bifida, and in a recent case which was associated with hypertrichosis of the knees [28].



Fig. 16.7 Hypertrichosis of the eyebrows

16.4.1.3.1.2 Hypertrichosis of the Ears

This is a relatively frequent manifestation in men, and also in post-menopausal women, along with hypertrichosis of the nasal vibrissae; however, in order to consider this a type of hypertrichosis, it would need to be present from early childhood or adolescence.

16.4.1.3.1.3 Hypertrichosis of the Eyebrows

This hypertrichosis is usually present after adolescence in patients who usually have a great deal of hair on glabellar areas, even occupying the interglabellar area [12]. In order to establish the diagnosis of nevoid hypertrichosis, it is required that the hairs become coarse, hard and with an anagen prolongation as of adolescence, which accounts for their being very long and straight, which makes it impossible to hide them by "sticking" or combing them onto the glabellar areas (Fig. 16.7).

16.4.1.3.2 Hairy Polythelia

This is a lot more common than would appear, although there are few publications about it. It should be noted



Fig. 16.8 Hairy polythelia on left abdominal mammary line

that it has already been included in Kajawa's [37] classification of the eight types of supernumerary mammary tissue: (1) complete breast with nipple, areola, and glandular tissue; (2) glandular tissue and nipple; (3) glandular tissue and areola; (4) glandular tissue alone; (5) nipple and areola, with a fatty area replacing the mammary glandular tissue (pseudo mamma); (6) nipple alone (polythelia); (7) areola alone (areolar polythelia); (8) tuft of hair (*hairy polythelia*) (Fig. 16.8). However, in the most recent, by Urbani and Betti [92], *hairy polythelia* disappears, as they do not think that the follicular component should be called that and considered it as accessory mammary tissue. Along with González-Cámpora, I have been able to show that the presence of a "lock of isolated hairs" is, if nothing else, a marker of underlying mammary tissue, whether this is an areola or apocrine glandular parenchyma; therefore, we believe the name should remain [20]. This is presented in the form of a "tuft" of hairs, frequently symmetrically, along the "mammary crest or line," although its more common location is the abdominal area. There are cases of polythelia with various nipples along the mammary line, generally accompanied by a tuft of hair, and in the abdominal region [23]. Familiar cases may be associated with several abnormalities of the urinary tract, such as



Fig. 16.9 Anterior cervical hypertrichosis

ectopic kidneys [38, 88], thus they may be considered markers of *mammo-renal syndrome* and *acro-mammo renal syndrome* [93], or of *fetal alcohol syndrome* [40], although there are authors who insist that they may appear without any type of association in some geographic areas or races, such as the Semites [4]. At present, the discovery of any kind of supernumerary mammary tissue demands an investigation of the possible association with carcinoma of the testicle, urinary bladder, prostate, or renal adenocarcinoma [24]. There was a description of Paget's disease in association with a supernumerary nipple in an adolescent girl [61].

16.4.1.3.3 *Anterior Cervical Hypertrichosis*

We have decided to consider this form, which we described many years ago [12] and for which retrospectively several families have been reported [57]. The mode of inheritance is most likely autosomal recessive [94]. Our cases included a woman and three of her daughters who have decreased touch and pain perception on their anterior cervical surface (Fig. 16.9). We did not perform biopsy given the patients' refusal; therefore, we could not associate this hypertrichosis with undermining abnormalities such as nevus or neurological alterations. A publication in 1991 [89] concerns an Arab family in which three members presented with anterior cervical hypertrichosis associated with motor and peripheral sensory neuropathy, two with ocular albinism, and five with thalassemia minor, with hypertrichosis and neuropathy coinciding in two of the latter group. This association (OMIN: 239840) is considered to be an autosomal-recessive trait [94]. In the last family [57] no association with peripheral neuropathy was observed. Idiopathic non-familial anterior cervical hypertrichosis without associated abnormalities have been also described [94].

Posterior cervical hypertrichosis on the cervical vertebrae has been also described [94]. It is an X-linked or autosomal-dominant trait. It has also been associated with underlying kyphoscoliosis (OMIM: 117850) as an autosomal-dominant disorder [77].

16.4.1.3.4 Primary Multifocal Localized Hypertrichosis

We described in 2001 [36] a particular type of localized multifocal hypertrichosis on the trunk and arms of a 41-year-old woman, with partial diffuse woolly hair and symmetrical and circumscribed allotrichia in the periauricular areas, and her 12-year-old son who had congenital triangular temporal alopecia and partial diffuse woolly hair. We proposed the term "primary localized multifocal hypertrichosis" for these cases because the excessive growth of hairs did not occur on the entire skin surface, only on the upper part of the trunk and arms in several foci (Fig. 16.10). As there was no association with an underlying defect, it was considered to be a primary hypertrichosis. Hypertrichosis does not tend to improve with age.



Fig. 16.10 Primary multifocal localized hypertrichosis

16.4.1.3.5 Secondary Nevoid Hypertrichosis

These are associated with abnormalities of the fat, muscle, bone, or of the underlying hemodynamic system [30]. The cases with fat abnormalities have hypertrichosis associated with lipodystrophy; those with muscular abnormalities have hypertrichosis with hemihypertrophy; those with bone abnormalities have hypertrichosis with scoliosis; and the cases with hypertrichosis and associated hemodynamic abnormality have shortened limbs with a venous hypertrophy [30], or limb growth with an arterial hypertrophy. Hypertrichosis has been also described to occur in fibrous hamartoma of infancy, although this association was only described in three cases [100]. Mild hypertrichosis, pronounced skin induration, and limited joint mobility characterize Stiff skin syndrome [39].

Hypertrichosis on plexiform neurofibromas of von Recklinghausen's disease has also been described (Fig. 16.3).

16.4.1.3.6 Nevoid Trichostasis Spinulosa

"Trichostasis spinulosa" can present with a nevoid distribution on a seborrheic area, such as the interscapular areas and the mid-back, sometimes related to intradermic melanocytic nevi or other dermatoses such as Darier's disease. Clinically this appears as a slightly pigmented patch in which one can see accumulations of follicular papules with telogen hairs retained within a follicular pore. As is the case in simple trichostasis spinulosa, the hair retention is due to the agglutination of the hairs formed in successive cycles, inside the follicle. This agglutination is a consequence of the increase in sebum or oils or hydrocarbons that have been applied to the skin. Other etiopathogenic theories include the presence of multiple congenital papillae, which would relate this process with *pili gemini*, follicular damage due to external irritants, or an increase in the normal cycle of the follicle. The differential diagnosis with keratosis pilaris and with eruptive vellous hair cysts must be made [52].

16.4.1.4 Spinal Dysraphism

The term dysraphism means "alteration in the formation of a fold or elevation which is constituted in the midline of the human body as a consequence of the union of two lateral portions." There are, therefore, dysraphisms of the penis, testicles, vertebral column, etc. That of the vertebral column is known as "spinal" and this is the one we shall refer to.



Fig. 16.11 Fawn tail as a marker of spina bifida



Fig. 16.12 Hypertrichosis on the right forearm that was covered for a month with a plastic splint for a Colles' fracture

These are usually located in the dorsal mid-line, and they "mark" a hidden vertebral defect that is the consequence of an embryological failure in the separation of the neuroectoderm from the epithelial ectoderm [1]. The *"fawn tail"* is usually a marker for spina bifida occulta or for diastematomyelia, which is why it is usually located at the lumbar or the sacral level (Fig. 16.11), where failure of the vertebral raphe to close is most often seem. This hypertrichosis may mark the existence of a "dermal sinus tract," a diastematomyelia, a "filum terminale," a lipomyelomeningocele, a myelomeningocele, a neurofibroma, and a meningioma [25, 69].

Spinal dysraphism is usually four times more common in girls than in boys. Sometimes, instead of the "fawn tail," there may be other stigmas, such as port-wine hemangioma, telangiectases, lipoma, fibroepithelial polyp, benign or malignant neoplasias of the ependymoma type, neurofibromas, melanocytic nevi, nevus comedonicus [33], teratomas, or other unclassified hamartomas, dyschromic elements (either hypo- or hyperpigmented), connective tissue nevus, scars, skin aplasia, dermal depression, or "sinus" [25]. With respect to the latter, Yabe and Furukawa [99] note that, although these may be congenital, there are also acquired forms. At other times, this is manifested by a pilonidal fistula, with a tuft of hair inside, instead of by a "sinus." This fistula, and sometimes a "pilonidal cyst," may go unnoticed, and only become evident following trauma, for example in harsh mounts onto off-road vehicles, horses or bicycles [64].

If there is traction on the spinal cord, there is slowly progressive muscle weakness in the legs, and a loss of both sensation and sphincter control. If there is transfixing of the spinal cord by bone specula, known as "diastomyelia," this is an indication for surgery.

When a sequestrated meningocele is located in the scalp, the marker may be a plaque of alopecia, sometimes surrounded by fine hypertrophic hairs, and in one case there was a faun's tail in the center of the alopecic plaque [55].

16.4.2 Acquired Localized Hypertrichosis

These are seen as a result of multiple direct cutaneous traumas; that is to say, after repeated friction, irritation, or inflammation, the hair of that area becomes longer and thicker. The classic examples are "hypertrichosis of the back in sack carriers" [12], and the "hypertrichosis of the fractured limb after the application of plaster splints" (Fig. 16.12) [17]. However, it should be remembered that this may appear in chronic inflammatory processes such as repeated erysipelas [12], legs with chronic venous insufficiency, thrombophlebitis, areas of erythema nodosum [7], on inflamed knees due to gonococcal arthritis, or chronic osteomyelitis, peripheral neuropathies, scratch areas due to an itching dermatitis of the lichen planus type, or due to the pinching habits such as those seen in people with an abnormally low IQ.



Fig. 16.13 Localized hypertrichosis on a bufaloid neck characteristic of the "costaleros" that bear the "pasos" in Spanish Holy Week

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Transitory localized hypertrichosis has also been seen at vaccination sites, areas of wart excisions, chicken pox scars, on the periphery of burns, insect bites, melorheostatic linear scleroderma, in contact dermatitis secondary to the application of dinitrochlorobenzene, and croton oil, and secondary to herpes zoster in a dermatome [98]. I described the presence of hypertrichosis on the "buffaloid" muscular mass which is developed by the *"costaleros"* who bear the "pasos" the Holy Week of Seville (Fig. 16.13), something that is quite common [15].

16.5 Symptomatic Hypertrichosis

16.5.1 Hypertrichosis in Congenital and Hereditary Diseases

There are many genodermatoses which are characterized by the presence of hypertrichosis as the main or secondary diagnostic symptom. Below the most common are reviewed (Table 16.3).

16.5.1.1 Lipoatrophy (Lawrence-Seip Syndrome)

This is characterized by the complete loss of the subcutaneous adipose tissue, which is always evident before the age of 2, hepatomegaly, splenomegaly, hyperlipemia, xanthomas, and excessive bone growth and clitoris growth, with genital precocity. The hypertrichosis is visible from birth, although it becomes more evident with age, especially on the face, where the hairs on the head merge into those of the eyebrows and cheeks. There is also hypertrichosis on the neck, arms, and legs. Later insulin-resistant diabetes mellitus may appear.

When this is accompanied by acanthosis nigricans of the axillae, wrists, and malleoli, it is known as "Berardinelli syndrome."

16.5.1.2 Cornelia de Lange Syndrome

This is also known as *Brachmann-de Lange syndrome*. These children have a low birth weight, and are short of stature, which becomes more evident as they age demonstrating dwarfism. There are respiratory difficulties,

Table 16.3 Hypertrichosis in congenital and hereditary diseases

Lipoatrophy (Lawrence-Seip syndrome)
Cornelia de Lange syndrome
Craniofacial dysostosis
Winchester's syndrome
Rubinstein-Taybi syndrome
Mucopolysaccharidoses
Dystrophic epidermolysis bullosa
Porphyrias
Ostheochondrodysplasia
Gingival fibromatosis
Globoid leukodystrophy (Krabbe disease)
Piebaldism
Waardenburg's syndrome
Hammerschlag-Telfer syndrome
Dystrichiasis-lymphedema syndrome
Oliver-MacFarlane syndrome (trichomegaly syndrome)
Ito's type incontinentia pigmenti achromians

frequently a cognitive deficit, and a characteristic face with a small nose, low ear implantation, prominent *philtrum*, commissures of the mouth inclined downwards, widely spaced teeth, confluent eyebrows, hypertrichosis which includes long, curly eyelashes, and a low hair implantation line on both the forehead and the neck. The hypertrichosis is also visible on the back, shoulders, and extremities. There may be other ocular and skeletal malformations, such as a small head, developmental abnormalities of the hands and the feet, and hyperextensibility of the phalanges, with the shortening and widening of the first metacarpals being very typical. Occasionally one can see hypoplastic nipples and genitals [13]. Biochemically they show hyper-glutamicacidemia, hypoaminoaciduria, and an increase in the serum level of alpha-ketoglutarate [66].

16.5.1.3 Craniofacial Dysostosis

True craniofacial dysostosis, or Crouzon's syndrome, presents only as orbital, cranial, and facial malformation, which is why this new association of hypertrichosis of the face, arms, legs, and back, along with the persistence of the ductus arteriosus, and hypoplasia of the labia majores, should at least be considered as a variant thereof.

16.5.1.4 Winchester Syndrome

This is characterized by the presence of dwarfism, joint destruction, corneal opacities, osteolysis of the carpal and the tarsal bones, osteoporosis, and a thickened and hyperpigmented skin with hypertrichosis [13].

16.5.1.5 Rubinstein-Taybi Syndrome

The most characteristic malformations of the syndrome, next to the mental deficiency, are dwarfism, the presence of broad and large big toes, and a "bird face" with an antimongoloid palpebral fissure, high-arched palate, pointed nose, irregular teeth, and low implantation of large ears [13]. It has also been described in association with piebaldism [46]. In 64% of cases one can see hypertrichosis of the trunk, limbs, and face, with a low frontal hair implantation line.

16.5.1.6 Mucopolysaccharidoses (MPS)

All of these are deposits of mucopolysaccharides in various tissues, including the dermal papilla, which accounts for the hypertrichosis, and mucopolysaccharidiuria. There are eight forms, and with the exception of MPS II or Hunter's syndrome, which has a recessive sex-linked inheritance pattern, all are autosomal-recessive trait.

MPS I is really three syndromes: (1) MPS IH, or Hurler's syndrome, characterized by a coarse face with thickened and dry skin, and hypertrichosis on the face, trunk, and extremities that becomes evident after 18–24 months; (2) MPS IS, or Scheie's syndrome, which corresponds to the old MPS V, and at present is considered to be a "frustrated" form of Hurler's syndrome; and (3) MPS IHS, or Hurler-Scheie's syndrome, which has hypertrichosis similar to previously named syndromes. In all three forms there is a defect of α-L-iduronidase.

The other autosomal-recessive mucopolysaccharidoses are: MPS III, or Sanfilippo's syndrome, characterized by hypertrichotic children with serious mental retardation, but few somatic alterations; MPS IV, or Morquio's syndrome, which defines children with metachromatic inclusions in the leukocytes and ocular, cardiac and skeletal alterations, among which one notes a short neck and barrel chest; and MPS VI, or Maroteaux-Lamy's syndrome, in which the children present with dwarfism from the age of 2–3 years, lumbar kyphosis, protrusion of the sternum, and a Hurler-type face. These three MPS are very rare, and MPS VII and VIII are even more so.

MPS II, or Hunter's syndrome, has two forms. One is less severe, in which the patients present pigmentary changes on fundoscopy, with a loss of visual acuity, lumbar kyphosis, dwarfism, progressive deafness, hepatosplenomegaly, coarse face, short neck, sclerodermiform infiltration of the extremities, multiple ivory-white papules in the subscapular and other body areas, and hypertrichosis. The other is the severe form, which, in addition to the above, presents with hydrocephaly, diarrhea, hoarseness, respiratory difficulty, and degenerative arthritis. The progressive neurological deterioration leads to death [13]. The hypertrichosis appears from 2–4 years of age.

16.5.1.7 Dystrophic Epidermolysis Bullosa

Classically, the presence of hypertrichosis of the face and the extremities has been noted in patients with dystrophic epidermolysis bullosa, whether these are dominant or recessive forms [17]. It seems logical that in these dermolytic genodermatoses there would be hypertrichosis, as a consequence of the constant inflammation and scarring to which these areas are subjected; that is to say, these would be secondary hypertrichoses. In this epidermolysis one can see perinuclear stellate bodies composed of collagen type VII, retained by the epidermis. When the activity of the disease remits, these bodies disappear [44].

16.5.1.8 Porphyrias

One can see hypertrichosis in five types of porphyria, always in areas exposed to sunlight, as this is related to photosensitivity:

1. *Erythropoietic porphyria (Günther's disease).* This is an autosomal-recessive genodermatosis, with mutation in the gene that codifies uroporphyrinogen-III synthetase. Peculiar to infancy, it is characterized clinically by the presence of "erythrodontia" as a consequence of the deposit of porphyrins in the enamel and the dentine of the teeth, which gives them a dirty yellow or brown color in sunlight, and a brilliant red color with Wood's lamp, red urine, and early photosensitivity which leads to burns, painful erythema, pruritus, blisters, and erosions that leave scars, hyperchromias, hypertrichosis (Fig. 16.14), and, if there is no photoprotection, there is mutilating sclerosis [51], loss of nails, reabsorption of the distal phalanges, syndactylia, ulceration, and contractures with destruction of the nasal and auricular cartilage, cicatricial alopecia, ectropion, keratoconjunctivitis, cataracts, and blindness. All patients present with hemolytic anemia and splenomegaly.

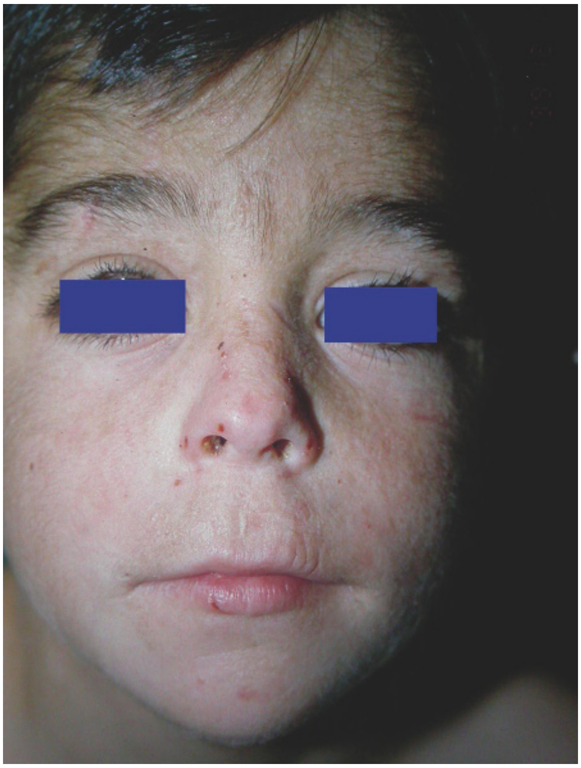


Fig. 16.14 Hypertrichosis in cheeks and forehead of a boy erythropoietic porphyria (Günther's disease)

2. *Erythropoietic protoporphyria.* This is due to deficiency of the enzyme ferrochelatase, which determines scarce use of, and therefore an increase in, the protoporphyrins, which leads to an excess thereof in the blood and also in the feces, absorbing light energy of 320–400 nm, which is the cause of the symptomatology. Clinically it is seen that at the age of 3–4 years, after exposure to sunlight, the child experiences a burning feeling, pruritus, or pain in the areas exposed to sunlight, and, later on, there is the appearance of erythematous, erythematopurpuric, or vesiculo-bullous elements, which, on rupturing are followed by scabs (frequently impetiginized), ulcers, and scars on the tip of the nose, cheeks, and backs of the hands. The skin turns yellow, with a large amount of folds and varioliform scars, and with hypertrichosis of the forehead and the limbs.
3. *Hepato-erythropoietic porphyria.* Described by Piñol in 1969, it is now known that this is a homozygotic form of porphyria cutanea tarda, with a deficiency of the enzyme uroporphyrinogen decarboxylase. Clinically it is characterized by dark urine from birth, and photosensitivity with marked intolerance to light, which leads to blisters, burns, scars, mutilations, and, especially, to hypertrichosis of the face and other exposed areas, which gives these patients a "simian aspect." There are no fluorocytes, or erythrodontia, and the photosensitivity improves with age [58].
4. *Porphyria cutanea tarda (PCT).* It is so called because this disease has many cutaneous manifestations, and these appear after the fourth decade of life. It is produced by two possibilities, although here we are only interested in the autosomal-dominant forms with a deficiency in uroporphyrinogen decarboxylase; the other form, caused by estrogens, ethanol, or hydrocarbons, shall be dealt with in Sect. 16.5.2.1. The enzymatic defect causes an increase of uro and copro I in the urine, which gives it a "Coca-Cola" color, and isocoproporphyrins in feces. The clinical picture is diagnostic, as there is skin fragility, which, on exposure to sunlight and trauma, shows the appearance of erosions and small blisters *(bullosis actinica et traumatica)* in uncovered areas, which on rupturing lead to scabs, scars, and milium cysts. Moreover, one can see hyperpigmentation, skin aging with thickened skin and facial hypertrichosis in the same places. There was a case of PCT whose only clinical manifestation was facial hypertrichosis [10]. Other, less frequent manifestations are the scleroderma-type lesions, porphyrinic alopecia, and the centrofacial lymphangiectases, in addition to the non-cutaneous symptomatology. Porphyria cutanea tarda is associated in 5%–16% of cases with hepatocellular carcinoma [58] and has been also related to hepatitis C infection [47].

5. *Variegate porphyria.* This is a congenital defect of protoporphyrinogen oxidase. This is a mixed porphyria in which patients have cutaneous manifestations similar to those of PCT.

16.5.1.9 Osteochondrodysplasia

In osteochondrodysplasia, hypertrichosis is associated with different skeletal abnormalities, among which one should note a narrow thorax with abnormalities of the ribs and the vertebrae, and cardiomegaly.

16.5.1.10 Gingival Fibromatosis (OMIN: 135400)

This is associated with hypertrichosis and epilepsy; that is to say, the same picture as that caused by the hydantoins. Inheritance is autosomal dominant. The hypertrichosis may be present at birth or can develop during early infancy, but in up to half of cases, it begins during puberty. It is more evident on the face, upper limbs, and the middle of the back in an identical distribution to hypertrichosis lanuginosa [94]. The gingival hyperplasia is almost always seen after the age of 10, although there are cases of epilepsy that can be seen as early as in infancy. The gingivae are pink, firm, pebbly or nodular in appearance. Failure of the teeth to erupt may be associated with periodontal abscesses.

16.5.1.11 Globoid Leukodystrophy (Krabbe Disease)

This is a very rare autosomal-recessive genodermatosis, which is fatal before the age of 2 and which presents with demyelinization and hypertrichosis.

16.5.1.12 Piebaldism

This is an autosomal-dominant genodermatosis characterized by circumscript hypopigmented areas, especially on the medial portion of the forehead, generally with a small, mottled section of normal pigmentation inside [13], associated with a white lock of hair located frontally. A heterozygous mutation of the *c-kit* gene encoding mast cell-stem cell growth factor receptor induces piebaldism [87].

16.5.1.13 Waardenburg's Syndrome

This is a form of piebaldism that is associated with perceptive deafness, dystopia cantharum with lateral displacement of the medial canthi, hypertelorism, heterochromia of the iris, and diverse bone alterations [13]. The white forelock is present in 20% of cases.

16.5.1.14 Hammersehlag-Telfer Syndrome

This is piebaldism associated with neurological defects such as cerebellar ataxia, motor incoordination, and deafness.

16.5.1.15 Districhiasis-Lymphedema Syndrome

This is a hereditary lymphedema that is associated with a pterygium on the neck, vertebral abnormalities, ectropion, and palpebral ptosis, and a characteristic “double row of eyelashes” [42].

16.5.1.16 Oliver-McFarlane's Syndrome (Trichomegaly Syndrome)

There is physical and mental retardation, pigmentary degeneration of the retina and the eyelashes, and very long eyebrows which need to be cut periodically, contrasting with an especially notable hypertrichosis on the occipital area [42].

16.5.1.17 Ito's Type Incontinentia Pigmenti Achromians

Ito's type achromians IP (hypomelanosis of Ito) has been described in association with hypertrichosis of the pubic area since birth, although there is no relationship with early puberty. Previously this has also been described in association with facial and generalized hypertrichosis [6].

16.5.2 Acquired Hypertrichosis

This is always a symptom or a consequence of several physiological or pathological situations, whether cutaneous or systemic.

16.5.2.1 Symptomatic Porphyria Cutanea Tarda

As we have noted before, this is the consequence of the ingestion of hexachlorobenzene (Turkish porphyria), and other drugs. The hypertrichosis is more noticeable than in PCT, to such a degree that in Turkey the affected children have been called "monkey children." It may also be caused by alcohol and contraceptives, with this first being seen in the children and then in the mother [48]. This type of porphyria may also be a paraneoplastic dermatosis caused by tumoral enzymes or alterations of liver cells due to several types of carcinoma.

16.5.2.2 Cerebral Alterations

There are some publications [17] that refer to hypertrichosis 1–4 months after a cranial trauma, especially in children, characterized by the presence of hairs on the forehead, cheeks, back, and extremities, occasionally asymmetrical, with this being most marked at the site of the greatest cerebral damage.

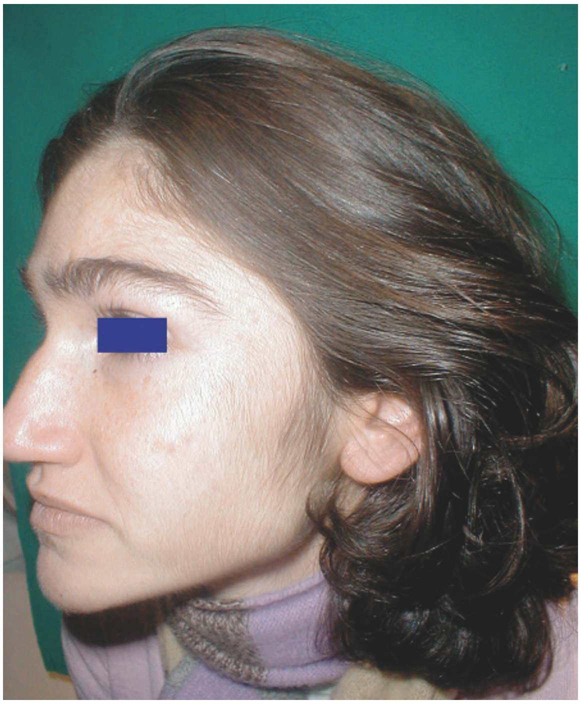


Fig. 16.15 Hypertrichosis on forehead and preauricular in anorexia nervosa

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16.5.2.3 Syringomyelia and Other Neurological Lesions

There have been descriptions [17] of asymmetrical hair growth in patients with syringomyelia and hypertrichosis, and there may also be asymmetry in patients with neuritis and multiple sclerosis.

16.5.2.4 Anorexia Nervosa

The patient is usually a young woman who restricts her dietary calorific intake, which may lead to emaciation. In about one-fifth of patients with this disease, hypertrichosis presents on the face (Fig. 16.15), trunk, and arms. These features are accounted for by the hypothalamic alterations suffered by those affected.

16.5.2.5 Malnutrition

In this disease as well as in malabsorption and celiac disease, there is usually hypertrichosis in children. Lanugo hairs sprout on the face and trunk, which may measure up to several centimeters in length, and these disappear when an adequate diet is eaten.

16.5.2.6 Acrodynia

A hypertrichosis, mainly facial, of the "billy goat type" beard has been described in patients with acrodynia (pink disease). On other occasions the hypertrichosis has been seen on the trunk and the extremities, with this being discreet on the face, where dense eyebrows with a tendency to join are sometimes the only trichological manifestation.

16.5.2.7 Dermatomyositis

Dermatomyositis in children generally only presents a picture that is similar to that in adults, although there is a greater incidence of calcinosis (Brunstig type), or a more acute and fulminant course due to vasculitis (Banker type). Moreover, it should be kept in mind that 95% of the children present with Gottron papules on the elbows, hands, and knees; 75% present with heliotrope erythema, and in many cases there is hypertrichosis on the face and extremities [74].

16.5.2.8 Hypothyroidism

The deficiency of thyroxin causes myxedema, which is a mucinous edema of the dermal tissue due to the extracellular deposition of a mucopolysaccharide–protein complex. Juvenile hypothyroidism is characterized by diffuse alopecia of the scalp, and hypertrichosis on the back, shoulders, and limbs, as a consequence of the prolongation of the anagen phase in the absence of the thyroid hormone. In congenital hypothyroidism the hypertrichosis localizes on the face.

16.5.2.9 Pretibial Myxedema

Some 4% of hypothyroid patients, especially after intervention, present with plaques or nodules of pretibial myxedema, and 40% of these also show exophthalmos and acropachy (Diamond's syndrome). Hypertrichosis is seen on the nodules, and is apparently due to the local effect of the myxedema on the dermal papilla.

16.5.2.10 Fetal Alcohol Syndrome

Children of chronic alcoholic mothers are small, microcephalic, with a physical and a mental retardation, and they present with heart and joint defects along with a characteristic face with a prominent nose, short palpebral fissures, maxillary hypoplasia, and hypertrichosis.

16.5.2.11 POEMS Syndrome

POEMS syndrome, or Crow–Fukase syndrome, is a rare entity characterized by the association of peripheral neuropathy of the sensory-motor polyneuropathy type (P), organomegaly (O), one or more endocrinopathies (E), the presence of monoclonal gammopathy (M), and skin changes (S). Among the latter, the most frequent are hyperpigmentation, which is present in 90% of cases; edema, in 80% of cases; and hypertrichosis in 71% of cases. The hypertrichosis is usually acral, especially on the lower limbs [71].

16.5.2.12 Acquired Immunodeficiency Syndrome (AIDS)

We shall finish with trichomegaly of the eyelashes [54], which can be seen in acquired immunodeficiency syndrome (AIDS). Although at first it was thought that this might be a marker of AIDS, it is now known that it only occurs in those patients who are resistant to zidovudine, and control of the infection with other antiretroviral agents makes the trichomegaly regress. Straightening of black people's hair with AIDS has also been described [75, 81]. Other trichological manifestations in AIDS include telogenic effluvium, premature balding, trichorrhexis nodosa, and alopecia areata [41].

16.5.3 Iatrogenic Hypertrichosis

Hypertrichosis determined by drugs is a frequent pathology related to the constant introduction of new drugs. Often the term hypertrichosis is confused with the term "drug hirsutism," when in fact this should be clearly differentiated, as the latter is the appearance of hair on androgen-dependent areas, while in hypertrichosis there is usually an increase in the length and the thickness of the vellous hair in those areas where it normally grows [84]. The hair that grows as a consequence of the action of a drug has a medium thickness, that is to say somewhere between vellous and terminal hair, and its growth is slow, it often taking weeks or even years before the patient is aware of this. It appears, or becomes more evident on the forehead and the temporal areas, and it increases in number and length on the flexor surfaces of the forearms, legs, and trunk. The axilla and the pubic areas are not affected. Drug hypertrichosis is usually, although not always, reversible within a few months of discontinuing the drug.

In accordance with the earlier definition of drug-related hypertrichosis and hirsutism, we consider that drugs responsible for the former are those which cause

Table 16.4 Most frequent drugs that produce hypertrichosis

• Antibiotics	• Streptomycin
• Anti-inflammatory drugs	• Benoxaprofen • Glucocorticosteroids
• Vasodilators	• Diazoxide • Minoxidil
• Diuretics	• Acetazolamide
• Anticonvulsants	• Phenytoin (diphenylhydantoin)
•	• Ciclosporin • Tacrolimus
• Psoralens	• Trimethylpsoralen • Methoxypsoralen
• Antiseptic agents	• Hexachlorobenzene
• Chelators	• Penicillamide

Table 16.5 Other drugs that can produce hypertrichosis

Ovulation simulators	Clomiphene
Antivirals	Amantadine Zidovudine
Anticonvulsants	Clonazepam Ethosuximide Lamotrigine (<1%) Methsuximide Tiagabine (<1%)
Antihistamines	Cetirizine (2%)
Antidepressants	Citalopram Clomipramine Fluoxetine Lorazepam Prazepam Quazepam Sertraline (<1%) Triazolam Venlafaxine (<1%)
Anti-glaucoma agents	Latanoprost
Antihyperlipidemics	Gemfibrozil
Antianemias	Epoetin, alfa
Biologic response modifiers	Interferons, alfa
Anorexiants	Dexfenfluramine (<1%)
For Alzheimer disease	Donepezil
Antiparkinsonians	Pergolide Selegiline
Antipsychotics	Olanzapine Risperidone (<1%) Thioridazine
Antiarrhythmics	Amiodarone
Beta-adrenergic blocking agents	Betaxolol (2%)
Calcium channel blockers	Diltiazem Verapamil
Diuretics	Spironolactone
Antiadrenal and antineoplastics	Aminoglutethimide (1%–10%)
Estrogen replacements	Chlorotrianisene
Osteoporosis prophylactics	Diethylstilbestrol
Posterior pituitary hormone	Nafarelin
Retinoids	Isotretinoin
Antiurolithic	Tiopronin

Percentages signaled are indicated in Litt [59].

Other drugs responsible for hypertrichosis are indicated, occasionally with the percentage in which this side-effect is observed [16, 59]. It is interesting to comment on the eyelash hypertrichosis induced by latanoprost [27, 65, 85] or interferon [29, 67], especially pegylated-interferon [50]. Latanoprost is currently used in the treatment of eyelashes lost in alopecia areata with varying results.

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hair growth without an androgen-dependent action; that is to say, without altering any known hormonal mechanism. Therefore, there should not be any increase in testosterone, 5-α-DHT, and Δ-4-androstenedione in serum. In Table 16.4 the drugs most frequently responsible for hypertrichosis are detailed [16], and Table 16.5 lists other drugs that have the capacity to induce hypertrichosis [59, 91].

16.5.3.1 Antibiotics

16.5.3.1.1 Streptomycin

Children with tuberculosis treated with streptomycin showed hypertrichosis on the limbs, but this may spread to the rest of the body. It has not been proved that the drug is the direct cause, or whether this is due to patient susceptibility, as hypertrichosis of these characteristics has been also described in children with tuberculosis who did not undergo therapy with streptomycin.

16.5.3.2 Anti-inflammatory Drugs

16.5.3.2.1 Benoxaprofen

This has been withdrawn from pharmacies due to its multiple undesirable side-effects, which included a fatal cholestatic jaundice [84]. Occasionally there have been cases of hypertrichosis due to its effect in association with a phototoxic action.

16.5.3.2.2 Glucocorticosteroids

Although according to the previous definition, all these cases could be considered to be "hirsutism," it has been shown that in certain cases, when high doses of glucocorticosteroids (cortisone) are administered for long periods of time, there is hair growth without the androgenic location visible in Cushing's syndrome, especially in children on the back. This is probably due to the direct conversion of the hairs in the telogen phase to the anagen phase, which is caused by certain adrenal hormones. Hypertrichosis can also be seen with topical glucocorticosteroids after prolonged treatment, especially in children [45].

16.5.3.3 Vasodilators

16.5.3.3.1 Diazoxide

This has a close chemical relationship with thiazide diuretics. It is a relatively weak inhibitor of the responses of the smooth muscle to several stimulants, including noradrenalin and angiotensin. This causes hypertrichosis without any signs of virilization in 50%–100% of the children treated, and, curiously, in fewer than 1% of the adults [84]. The hypertrichosis begins after 6 weeks of treatment, on the forehead, neck, back, thorax, and extremities. Biopsy shows a large number of follicles in anagen with increased glycogen content in the outer root sheath and a rich vascular network.

16.5.3.3.2 Minoxidil

This is a potent peripheral vasodilator which is reserved for the treatment of severe refractory hypertension, also called "malignant" hypertension, as this is a form of hypertension which progresses rapidly, and is often fatal. It is known that minoxidil increases the blood flow to epidermal cells, and, moreover, that it has a direct stimulating effect on them, causing hypertrophy of the existing follicles, but never follicular neogenesis, which is why this drug is not effective in long-standing androgenetic alopecias (AGA), or in stabilized advanced stages, in which the follicles have atrophied. Hair growth is very obvious on the face, the arms, and the legs of women. For some authors the hypertrichosis seen in women treated with minoxidil is clearly related to the amount of drug applied, while for others this would depend more on particular sensitivity to the minoxidil absorbed systemically by the hair follicles in these areas [68], and the effect disappears, although slowly, when drug application stops. In this way it has been shown that women who used 5% minoxidil and who developed hypertrichosis on the face, forearms and legs lost the hair on their face and forearms after 1–3 months, but that it took 4 or 5 months for the hair on their legs to disappear [68]. Recent clinical trial in females using 5% or 2% minoxidil, or 2% vehicle demonstrated that 20% (49/242) and 9% (21/237) of females using minoxidil 5% and 2% respectively developed hypertrichosis, and only 5% using vehicles [26]. The areas with excessive hair growth were the face/cheeks or chin, upper lip, forehead, eyebrows, neck, back of hands, arms, legs, and chest but there were no reports of generalized hypertrichosis. The mechanism for minoxidil-mediated facial hypertrichosis is unknown but the most plausible explanation would be the inadvertent transfer of topical minoxidil remnants to sites other than the scalp [26].

16.5.3.4 Diuretics

16.5.3.4.1 Acetazolamide

This is a sulfonamide that is characterized by being an inhibitor of the enzyme carbonic anhydrase. This reduces intraocular pressure, which is why it is used to treat glaucoma, and it acts as a diuretic. Hypertrichosis has been described in a child [12].

16.5.3.5 Anticonvulsants

16.5.3.5.1 Phenytoin (diphenylhydantoin)

This is a potent drug with anti-arrhythmic and anticonvulsant effects, which causes hypertrichosis in 5%–12% of the epileptic patients treated with it [90]. The increase of hair takes place 2–3 months after beginning the treatment, and it is accompanied by acne and hyperpigmentation. The most frequent locations are the extremities and the trunk, although some women presented with significant growth in the area of the moustache and on the chin (Fig. 16.16). The axillae and the pubic area



Fig. 16.16 Typical hypertrichosis on chin in patient treated with diphenylhydantoins

showed no pre-puberty modification, which supports the theory that this drug's action is not dependent on androgens. This is one of the few drugs with which the hypertrichosis is permanent, although it does improve somewhat after discontinuation [16]. The increase in hair is not related to the dose, or to the serum levels of the drug, which is why it has been suggested that its effect is related to the growth that it causes in all components of connective tissue, including the follicular papilla, a theory that is based on the fact that the side-effects of the drug include gingival hyperplasia [59].

16.5.3.6 Immunosuppressives

16.5.3.6.1 Ciclosporine

This is a potent immune-suppressing agent, which affects the synthesis of immunological modulators of the interleukin-2 type, without suppression of the bone marrow, which is why it started out being used in bone marrow transplants, although nowadays it is widely used in psoriasis [2] with a PASI greater than 18, and for atopic dermatitis. Approximately 50% of patients present with reversible hypertrichosis, especially on the face and the upper part of the trunk. A fairly constant fact in the patients who use this is that they find less depilation of hairs, and that these grow more, which is explained by ciclosporin's stimulatory effect on epidermal and follicular keratinocytes [84].

16.5.3.6.2 Tacrolimus

As tacrolimus has a similar mechanism of action to ciclosporin, and conversion from ciclosporin to tacrolimus is usual [62], hypertrichosis is a frequent side-effect of this drug [32, 86]. Eyelash trichomegaly has been described in association with ciclosporin, and, on one occasion, with tacrolimus [96].

16.5.3.7 Psoralens

These cause local erythema with thickening of the corneal layer, an inflammatory reaction, and hyperpigmentation, due to the increase of melanin in the areas exposed to sunlight. Two medications are mainly used in dermatological therapy: 4,5,8-trimethylpsoralen (4,5,8-TMP), and 8-methoxypsoralen (8-MOP); both cause hypertrichosis as a side-effect.

16.5.3.8 Antiseptic Agents

16.5.3.8.1 Hexachlorobenzene

Exposure to this drug causes an increase in the amount of smooth endoplasmic reticulum in the hepatocyte, as well as activation of cytochrome P450 and of mixed-function oxidase. It was used in Turkey in 1954–55 as a fungicide in wheat, and the ingestion hereof caused more than 3000 cases of "toxic porphyria," with dark urine, significant photosensitivity, and the presence of a hypertrichosis, especially facial, although the extremities and the trunk were also affected in a manner which was much more obvious than that of other porphyries [84]. The hyperpigmentation due to the photosensitivity and the facial hypertrichosis led to the children suffering from this disease being called "monkey children." The majority of the patients improved once the ingestion of this drug stopped, although some worsened again in the summer.

16.5.3.9 Chelators

16.5.3.9.1 Penicillamine

This is a chelating agent that is used in the of rheumatoid arthritis, Wilson's disease, cystinuria, and intoxication with heavy metals, which cause eruptions due to

hypersensitivity of the morbilliform and urticariform types, in addition to hypertrichosis of the trunk and the extremities [84].

16.5.3.10 Anti-glaucoma Agents

16.5.3.10.1 Latanoprost

Latanoprost, an anti-glaucoma agent, induces eyelash hypertrichosis when applied in the eye [27, 65, 85]. This is reason why latanoprost is currently used in the treatment of eyelash alopecia in alopecia areata universalis.

16.5.3.11 Biologic Response Modifiers

16.5.3.11.1 Interferons

Alpha-interferon also causes hypertrichosis of eyelashes [29, 67], and pegylated-interferon [50] was reported to induce eyelid and eyebrow trichomegaly when it was used to treat chronic hepatitis.

16.5.3.12 Paradoxical Hypertrichosis after Laser Epilation

This mechanism is currently a well known adverse effect of post-laser hair removal although its occurrence is rare [1].

16.6 Treatment of Hypertrichosis

As hypertrichosis is an androgen-independent effect, it is not feasible to use systemic drugs. The therapies currently available to treat hypertrichosis are limited to bleaching, trimming, waxing, "depilation" with creams, plucking, shaving (which, as is well known, does not cause thickening or an increase in hair), electrolysis and hair removal with intense pulsed light and laser [17, 76, 94].

Bleaching is a painless procedure whose active ingredient is 6% hydrogen peroxide, which oxidizes and softens the hair. Trimming of the hair is a recommended method for localized or generalized hypertrichosis. Waxing methods employ cold, warm or hot wax. It is a painful process that causes discomfort, irritation or folliculitis that must not be used in children.

Within the cream depilatories, those with barium sulfate have been shown to be especially effective, although they may cause irritation, which does not occur with the "calcium thioglycolate" depilatory creams. The latter are recommended for the treatment of hypertrichosis induced by drugs, especially by minoxidil [84]. Chemical depilatories have several disadvantages such as risk of allergic contact dermatitis, an unpleasant odor, and being suitable only for small areas and expensive [94].

The methods known as "permanent hair removal" are electrolysis and laser hair therapy. Electrolysis may be performed by galvanic, thermolysis, and blend methods. Currently the most useful method is a blend that combines galvanic electrolysis and thermolysis. The main disadvantage of electrolysis is the pain and the risk of scarring. To reduce the discomfort, pre-application of ice packs, EMLA or 4% lidocaine (ELA-Max) must be used.

Various laser systems have been developed for epilation of unwanted hair: ruby, alexandrite, diode and Nd:YAG Q-switched or large pulsed [95]; this is in addition to epilight lasers, which are based on an intense pulsed non-coherent light source (IPL- Intensive Pulsed Light).

Recently, the use of 15% eflornithine hydrochloride cream, in a twice-daily scheme of application, was considered as a suitable alternative for facial hypertrichosis, whose safety and effectiveness has been demonstrated in double-blind studies [83]. We prefer to use eflornithine at 11.5% or 15% cream in the treatment of facial hirsutism combined or not with laser epilation [18].

Summary for the Clinician

Hypertrichosis is a condition that means the growth of hair of an excessive amount and thickness on any part of the body. The term is frequently confused with *hirsutism*, which should only be applied to "women with an excessive development of hair according to the male pattern; that is to say, hair growth in the woman due to androgen overproduction or increased end-organ sensitivity to androgen."

Hypertrichoses are classified as generalized, localized, and symptomatic. All can also be classified according to the age of onset as congenital or acquired. Generalized acquired hypertrichosis may be a paraneoplastic syndrome; for example, acquired hypertrichosis lanuginosa; or localized, the result of association with abnormalities of fat, muscle, bone or of the underlying hemodynamic system; or related to multiple direct cutaneous traumas. Currently, of the acquired symptomatic forms the most frequent are those related to medication or drug usage, known as iatrogenic hypertrichosis.

Long-term removal of unwanted hair is the objective. The available methods to treat the excessive hair include bleaching, physical and chemical depilatories, electrolysis, intense pulsed light therapy, and laser hair removal.

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Chapter 17

Hirsutism

Francisco M. Camacho-Martínez

17

Key Features

- Hirsutism is related to hormonal factors, mainly an increase in androgen levels.
- In females, the main sources of androgens are the adrenal glands (dehydroepiandrosterone sulfate; DHEA-S) and the ovaries (Δ-4-androstenedione): dysfunction of these organs must be excluded when a patient present with hirsutism.
- The pituitary, the liver, ectopic hormones, certain drugs, and peripheral failure to convert androgens into estrogens may also be causes of hirsutism.
- If minimal or no hormonal abnormalities are found, the patient will be diagnosed as having a constitutional hirsutism (SAHA syndrome) or a familial hirsutism.
- As a general rule whenever there is hirsutism that appears abruptly and evolves quickly, one must first suspect that there is an ovarian, adrenal or pituitary tumor.
- When the hirsutism is mainly localized to the areola and the lateral surfaces of the face and neck, the androgens usually have an ovarian origin, whereas if the location is central, with a distribution from the pubic triangle to the upper abdominal area, between the breasts, to the neck and the chin, the origin is usually adrenal.
- The Ferriman and Gallwey score reflects functional hirsutism when the score is greater than 8 and an organic hirsutism when the score is greater than 15.
- A correct biochemical evaluation must request levels of free testosterone, 5-α-dihydrotestosterone (5-α-DHT), DHEA-S, 17-β-hydroxyprogesterone, Δ-4-androstenedione, prolactin, sex hormone binding globulin (SHBG), 3-α-androstanediol glucuronide, and prostate-specific antigen (PSA), a marker of hyperandrogenism. In ovarian hirsutism and HAIRAN syndrome, we expand the laboratory evaluation to include luteinizing hormone (LH), follicle-stimulating hormone (FSH), LH:FSH ratio, and insulin levels.
- Depending on the origin of the hirsutism, the treatment is based on antiandrogens, glucocorticosteroids, and contraceptives, in association with topical and dermato-cosmetic therapies.

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17.1 Introduction

The term *hirsutism* defines the presence, in women, of hair and vellous hair with male characteristics and locations, whereas *hypertrichosis* is only an increase in the amount of hair.

Hirsutism is related to an increase in the androgen levels, which is why this cannot be seen before puberty. At puberty, the secondary sexual characteristics develop in men, leading to changes in the voice, palpable muscle mass, and the appearance of hair on the mustache, beard, thorax, shoulders, back, arms, thighs, pubic triangle, and buttocks. If this is seen in women, it means that there is an endocrinological alteration with an increased secretion of androgens by the ovaries or the adrenal glands [7, 26, 70]. Nevertheless, it is also possible that the androgen serum levels are normal and that the woman has hyperandrogenism symptoms. This is the reason why hyperandrogenism was defined as an increase in the concentration of androgens, or an exaggerated clinical response to the androgenetic action of glands [74]. The androgen responsible for the change in voice and the increase in muscle mass in women is testosterone, and that responsible for hirsutism and androgenetic alopecia is 5-α- dihydrotestosterone (5α-DHT) [10].

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17.2 Epidemiology

A large number of women visit physicians with this problem, to such a point that in a study of North American women, 35% of them presented with hairs on the linea alba, 20% on the thighs, 17% in the periareolar area, 16% in the lumbosacral area, and 10% in the upper pubic triangle [7]. In contrast, a european study demonstrated hirsutism in 1.2% of London females [26]. This difference relates to the definition of hirsute women: in the English study women were considered hirsute if they had a total Ferriman-Gallwey score greater than 10 [27]. In general, we admit that about 9% of the young female Caucasian population is hirsute [52] and that women from Southern Europe, specially the Mediterranean area, habitually present facial hirsutism [74].

17.3 Classification

We classify hirsutism into eight categories [7]. We will use this classification in the description of clinical types, diagnosis, and treatment [10, 8, 12].

1. *Hirsutism of a constitutional origin:* as women with this type of hirsutism also present with seborrhea, acne, and alopecia (which are androgen-dependent symptoms and entirely cutaneous), we must consider this syndrome as a "minor" form of hyperandrogenism syndrome [7, 9, 70], and the hirsutism that appears can also be called "dermatological hirsutism." This constitutional or "dermatological" hirsutism also used to be called "idiopathic" and "endogenous," but these terms are no longer used, as we did not know the origin of the increases in androgen levels. Nowadays we either know the source of the excess androgens, or why they act as if they were being produced in excess. We also know that when androgens act as if they were present in excess amounts, the problem is located in the effector organ, therefore some authors call this "peripheral hirsutism" [14]. Currently we accept the name "*SAHA syndrome*" proposed by Orfanos in 1982 [64], SAHA being the acronym of its four dermatological signs: *s*eborrhea, *a*cne, *h*irsutism and *a*lopecia [64].

   When there is a slight increase in androgens of adrenal origin, this is called "*persistent adrenarche syndrome.*" If the androgens come from the ovaries, this is known as "*excess ovarian androgen release syndrome.*" If a slight increase in prolactin is the only alteration found, the designation "*SAHA syndrome due*

to hyperprolactinemia" is used. If one cannot find any endocrinological alteration, the term "*familial hirsutism*" must be employed. This can reflect a familial increase in the end-organ response to normal plasma levels of androgens [14]. The HAIRAN syndrome has been recently described as a fifth variant [65].

2. *Hirsutism of pituitary origin*: an increase in adrenocorticotropic hormone (ACTH) causes hirsutism through hypercortisolism and a secondary increase in prolactin. Prolactin-secreting pituitary adenomas, psychogenic drugs, and contraceptive pills, among other factors, may cause this androgen hyperproduction [7, 14].
3. *Hirsutism of an adrenal origin:* this may be due to "hypercorticism," or to congenital or late-onset adrenal hyperplasia, with an increase of dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S).
4. *Hirsutism of an ovarian origin:* hyperthecosis, Stein–Leventhal's syndrome, and ovarian tumors lead to an increase in progesterone, Δ-4-androstenedione, and testosterone.
5. *Hepatic hirsutism:* a low level of sex hormone binding globulin (SHBG) leads to a larger amount of free testosterone, and the conversion to 5α-dihydrotestosterone (5α-DHT) may be greater. As SHBG is produced in the liver, in cases of liver disease there will be a decrease in the binding globulin [7, 14].
6. *Hirsutism due to ectopic hormones:* carcinoid tumor, choriocarcinoma, and metastatic lung carcinoma are capable of producing hirsutism.
7. *Iatrogenic hirsutism:* certain drugs may be the cause of hirsutism. Although the majority of drugs really cause hypertrichosis, anabolic steroids cause hirsutism when administered to women.
8. *Hirsutism due to peripheral failure in converting androgens into estrogens:* there is a conversion of androgens into estrogens, both in the ovaries and in the periphery. The main androgen that is transformed into estrogen is Δ-4-androstenedione, followed by testosterone. If there is a failure in the conversion of Δ-4-androstenedione to estrogens, there will be a greater amount of free Δ-4-androstenedione [7, 14].

17.4 Clinical Features

17.4.1 Constitutional or Dermatological Hirsutism (SAHA Syndrome)

This type of hirsutism appears in constitutional hyperandrogenism and can be accompanied by the presence of seborrhea, acne, and androgenetic alopecia, dermatological manifestations that are the result of the actions of androgens on target organs. The first sign to appear (and also the most frequent) is seborrhea, followed by acne, hirsutism, and alopecia. These four signs altogether are present only in the 21.5% of Caucasian women with SAHA syndrome [9].

We will consider five types of dermatological hyperandrogenism [8, 9, 12], because recently Orfanos et al. [65] described HAIRAN syndrome to be a fifth type of SAHA syndrome.

17.4.1.1 Excess Ovarian Androgen Release Syndrome (Ovarian SAHA Syndrome)

These are young women between the ages of 16 and 20, with pustular acne, mild lateral facial and mammary hirsutism (Fig. 17.1), female androgenetic alopecia (FAGA, Ludwig grade I), and intense seborrhea. They also have a tendency toward obesity. Menstruation may be normal or short and the cycles are often shorter than 28 days. There is a slight increase in the plasma levels of Δ-4-androstenedione and free testosterone, which produces an increase in 5-α-reductase activity. The level of SHBG is usually decreased and that of androstanediol glucuronide is increased [9, 10]. The remaining sex hormones and prostate-specific antigen (PSA) levels are normal [37].

17.4.1.2 Persistent Adrenarche Syndrome (Adrenal SAHA Syndrome)

These young women are very stressed, and they present with significant seborrhea, nodulo-cystic acne with scars on their face and back, FAGA I-II, or with male pattern (FAGA.M), and hirsutism with central predomi-



Fig. 17.1 Ovarian SAHA. Lateral mammary hirsutism, score 1

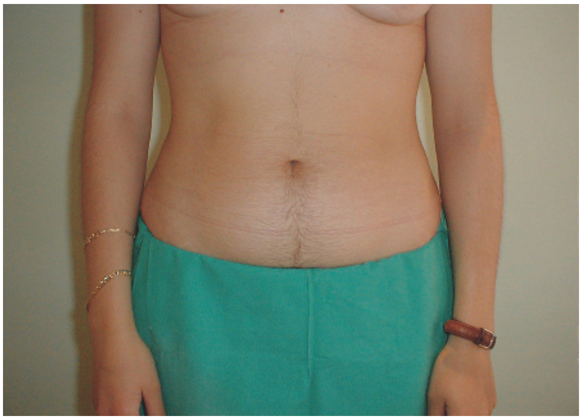


Fig. 17.2 Adrenal SAHA. Central hirsutism, score 2

nance, which joins the neck with the upper pubic area (Fig. 17.2). *Menstrual cycles are usually longer than 30 days*. In contrast with ovarian SAHA, these patients are usually thin and constantly stressed, presenting with severe palmar hyperhidrosis. Their menstrual cycles are generally longer than 30 days. Biochemically there is an increase in DHEA-S with normal levels of PSA, free testosterone, and 5-α-DHT [10, 37].

17.4.1.3 Hyperprolactinemic SAHA Syndrome

These hirsute women complain of central and lateral hairiness and oligomenorrhea, and sometimes nodulocystic acne, seborrhea, FAGA.I, and even galactorrhea. The prolactin levels may be slightly increased [9].

17.4.1.4 Familial Hirsutism

This is generally facial, as a prolongation of the preauricular hair implantation line (Fig. 17.3). It is not accompanied by other alterations of the SAHA syndrome, and laboratory tests are absolutely normal [9].

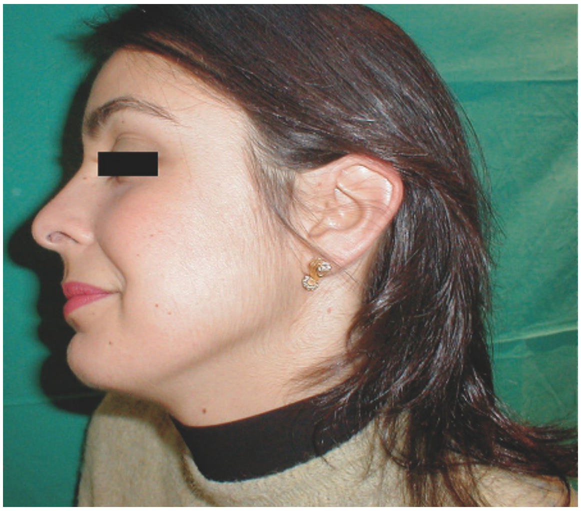


Fig. 17.3 Familial hirsutism



Fig. 17.4 HAIRAN syndrome. Lateral facial hirsutism and acanthosis nigricans on the lateral aspect of the neck

17.4.1.5 Familial Virilization (SAHA Type HAIRAN Syndrome)

This is a familial virilization syndrome characterized by insulin resistance (IR) and acanthosis nigricans (AN) that is found in 2%–5% of hirsute patients (Fig. 17.4) [65]. This syndrome, known as "HAIRAN," has similarities with polycystic ovary syndrome type 2, and is distinguished by the woman presenting with hyperandrogenism (HA), in association with insulin resistance (IR) and acanthosis nigricans (AN) [18]. Laboratory tests demonstrate the same alterations as in ovarian SAHA syndrome, with increased serum levels of insulin [18].

17.4.2 Adrenal Hirsutism

In a patient of any age with evident central hirsutism, who is thin, with a FAGA.I-II or FAGA.M.I-III, and with signs of virilization, the presumption should be that the origin of the androgens is adrenal [7, 70].

17.4.2.1 Non-Tumoral Adrenal Hirsutism

17.4.2.1.1 Adrenal Hyperplasias

17.4.2.1.1.1 Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) is due to a congenital deficiency of one of the enzymes involved in the synthesis of adrenal steroids. There is no direct synthesis of particular hormones, only a build-up of the intermediate product before the deficient enzyme in the pathway. As these intermediate products are not recognized by the pituitary, the feedback mechanism is not initiated, which results in very high levels of ACTH. Affected individuals are deficient in aldosterone, cortisol, and sex steroid [28].

17.4.2.1.1.2 21-Hydroxylase Deficiency

A deficiency of 21-hydroxylase is responsible for 95% of all CAH cases, and its variety of clinical manifestations relates to mutations of the CYP21B gene [58]. In general, its deficiency prevents the transformation of 17-hydroxyprogesterone to 11-desoxycortisol and of this to cortisol in the fasciculated and reticular areas of the adrenal gland, and of progesterone to 11-desoxycorticosterone and of this to aldosterone in the glomerular area. There are three clinical forms: the classic form or the "salt losing form," which is the most severe form; the non-classic virilizing form, which is moderate; and the late-onset CAH form (attenuated CAH), which is manifested only when demand for steroids increase at puberty or thereafter.

The virilization symptoms of the *classic form* or the *salt losing form* relate to the failure of aldosterone synthesis in the glomerular area; in addition there is an electrolytic disorder, similar to that seen in Addison's disease, with a loss of sodium in the urine, which leads to anorexia, lethargy, vomiting, diarrhea, and stabilization of the weight or weight loss, and hypertension.

The *non-classic form* or the *non-salt losing form* is accompanied by failure of cortisol synthesis in the fasciculated and reticular areas; it interests dermatologists because central severe hirsutism is its most evident symptom of virilization [58]. Hypertension may also be present. The absence of cortisol causes hyperproduction of ACTH, which will produce adrenal hyperplasia.

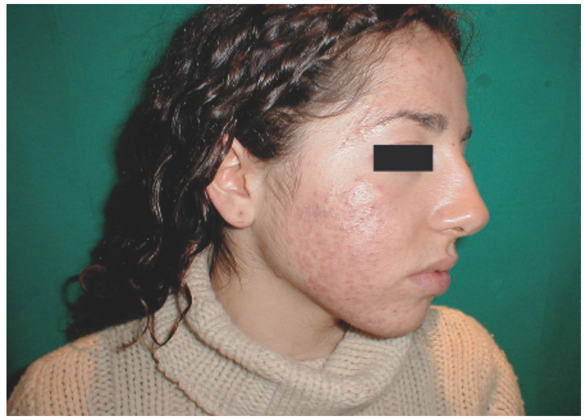


Fig. 17.5 Adrenal SAHA. Severe papulo-pustular acne and central hirsutism

These patients show premature growth of hair, leading to an early pubarche, which is soon followed by significant hirsutism, accompanied by severe facial papulo-pustular acne (Fig. 17.5) and the onset of alopecia. Oligomenorrhea, spaniomenorrhea (scanty menstruation), clitorimegaly, masculinization of escutcheon, changes in the tone of voice, decreasing or lack of breast development, and broadening of the shoulders as a consequence of increased muscle mass can be associated manifestations. Biochemical study shows high levels of progesterone, 17-hydroxyprogesterone and PSA, and low levels of cortisol, aldosterone and sex steroids [16, 28].

Late-onset congenital adrenal hyperplasia (*attenuated CAH)* is due to partial enzyme deficiencies of 21-hydroxylase, which are manifested when demand for steroids increases at puberty or thereafter. Virilization is again a clinical feature; however, 40% of patients have just hirsutism, another 40% a PCOS pattern, and 20% anovulatory cycles without hirsutism [58]. In cases of prepubertal acne, early pubarche, and premature bone maturation it is mandatory to carry out a hormone study because in a high percentage of these cases there is deficiency of 21-hydroxylase [7].

17.4.2.1.1.3 11β-Hydroxylase Deficiency

In *11β-hydroxylase deficiency* there is always hypertension and in the majority virilization [7]. Its deficiency prevents the transformation of 11-desoxycortisol to cortisol in the fasciculated and reticular areas, and of

11-desoxycorticosterone to aldosterone in the glomerular area. There is the potential to develop a "salt losing crisis" when under physiological stress [27], and a moderate or "late-onset form." Biochemically high levels of desoxycorticosterone, 11-desoxycortisol and PSA are found with minimal levels of aldosterone, cortisol and sex steroids [7, 16, 28, 53].

17.4.2.1.1.4 CAH by Absence of Other Enzymes

CAH by absence of other enzymes is uncommon, representing 1% of CAH. These deficiencies can be of 17-α-hydroxylase, 3-β-hydroxysteroid dehydrogenase, 18-hydroxylase, 18-hydroxysteroid dehydrogenase, and 21,22-desmolase, the last being incompatible with life [7].

17.4.2.1.1.5 Cryptic CAH

Cryptic CAH is a form of CAH that appears in family members of patients with CAH, who have the same biochemical alterations, but no clinical manifestations.

17.4.2.1.2 Endogenous Hypercortisolism (Cushing Syndrome)

Cushing syndrome may be associated with high plasma corticotropin (ACTH) levels (pituitary hyperproduction and "ectopic ACTH syndrome"), normal ACTH levels, or even with a complete lack thereof (adrenal hyperplasia, adenoma or carcinoma). In all cases, there is an increase in plasma cortisol, which is the cause of the clinical manifestations. In the case of adrenal hyperplasia there is an insidious onset of symptoms, but when it is due to a tumor the evolution is more rapid. If there is a significant production of androgens, which is not the usual case, there will be a virilization syndrome with hirsutism, FAGA.M, a deep voice, hypertrophy of the clitoris, and oligo/amenorrhea in addition to the typical cutaneous manifestations of Cushing syndrome, such as purplish striae, ecchymoses, facial acne, acanthosis nigricans, fungal infections, and hyperpigmentation, and other general symptoms such as centripetal obesity, moon facies, buffalo hump, apron abdomen, hypertension, steroid diabetes, asthenia, pain in the vertebral column and the neck due to developing osteoporosis, proximal myopathy, etc. [58, 76]. Biochemical screening always shows high levels of cortisol and PSA [16, 28, 53], leukocytosis with lymphopenia, a diabetic glucose tolerance curve, and hypokalemic and hypochloremic alkalosis [7].

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17.4.2.2 Tumoral Adrenal Hirsutism

A virilizing adenoma or carcinoma may be responsible for a severe hirsutism (Fig. 17.6), with acne, alopecia, amenorrhea, seborrhea, and clitoromegaly plus the other characteristic signs of Cushing syndrome. Adrenal tumors may secrete one or several hormones in excess; they directly produce large amounts of estradiol and alternatively Δ-4-androstenedione, DHEA ad DHEA-S.

17.4.3 Ovarian Hirsutism

If the patient presents a hirsutism greater than grade 2, which is predominantly lateral (i.e., on the face and the breasts), FAGA.I-II, acne, seborrhea, obesity, and obvious menstrual disorders, the presumed diagnosis is hirsutism of ovarian origin, which may also have tumoral or non-tumoral etiologies.

17.4.3.1 Non-Tumoral Ovarian Hirsutism

17.4.3.1.1 Polycystic Ovary Syndrome (PCOS)

This syndrome was described by Irving Stein and Michael Leventhal in 1935, and is characterized by infertility, secondary amenorrhea or menstrual alterations, and, occasionally, obesity in women with large poly-



Fig. 17.6 Adrenal tumor. Facial hirsutism, score 4 on the upper lip and the beard area respctively

cystic ovaries. The reported incidence ranges from 3% to 12% varying by the diagnostic criteria used and the population studied. There has been debate in the literature as to whether this represents a single disease or several phenotypically overlapping diseases [52]. For this reason, several authors prefer to name to the disorder "functional ovarian hyperandrogenism." However, we prefer to maintain the classical classification of type 1 or primary PCOS and type 2 PCOS that is secondary to pathological ovarian processes or to hormonal dysregulation in the hypothalamus, pituitary, and adrenal glands.

In primary PCOS a complex polygenetic heritable factor plays a role, with over a dozen candidate genes implicated in its pathogenesis. There is evidence to support an autosomal-dominant genetic model with low penetrance. Genes that have been postulated to be involved include the CYP17A gene, the CYP11A gene, the insulin gene, and variable-number tandem repeat/VNTR sequences. Mothers of women with PCOS have dyslipidemia, hyperandrogenemia, and serum markers of insulin resistance [72].

Secondary PCOS can be produced as a consequence of "ovarian SAHA syndrome" or "excess ovarian androgen release syndrome" that was not treated when the patient only had dermatological signs. Sciarra's team [80] demonstrated, in 1983, that in ovarian SAHA with hirsutism, the hyperandrogenism is slowly progressive from adolescence, with a first phase in which only peripheral androgenic metabolism alterations are observed; a second phase with adrenal gland changes that produce high levels of DHEA-S; and a third phase in which the adrenal hyperandrogenism continues the increase of peripheral aromatization of Δ-4-androstenedione with increased serum levels of estrone and LH as a consequence of an altered hypothalamic–pituitary–adrenal axis.

Hypothalamic dysfunction causes an increased pulse frequency of gonadotropin-releasing hormone that is responsible for the overproduction of LH and relative reduction of FSH with an increased LH:FSH ratio. This relative increase of LH causes the ovarian theca cells to synthesize androgens. Women with PCOS tend to be hyperinsulinemic and obese. Insulin plays a pathogenic role in PCOS, enhancing androgen production in theca cells and inhibiting hepatic synthesis of SHBG resulting in high levels of free testosterone. A severe variant or subphenotype of PCOS type 2 is HAIRAN syndrome in which hyperandrogenism is accompanied by insulin resistance and acanthosis nigricans [18].

The Rotterdam Consensus Group considers PCOS [45] when there are at least two out of three of the following criteria: (1) chronic oligoovulation or anovulation, clinically diagnosed as oligomenorrhea or amenorrhea, (2) clinical or biochemical evidence of hyperandrogenism, (3) polycystic ovaries demonstrated by ultrasound. A decrease of FSH level and an increase in LH level, previously considered as diagnostic, are not currently admitted as necessary. A woman with polycystic ovaries detected by ultrasound but without ovulatory disorder or hyperandrogenism should not be considered as having PCOS [52] although polycystic ovaries alone constitute a risk factor for developing PCOS.

Symptoms begin to manifest around menarche, sometimes presenting with premature pubarche. Oligomenorrhea is present in 75%–90% of patients and amenorrhea only in 30%. Infertility and irregular menses are common but not necessary for the diagnosis of PCOS. After a normal menarche, the patients develop a persistent amenorrhea associated with virilization and sterility. There are no signs of genital virilization. These patients have large ovaries with a pearly gray surface, a thickened capsule, and cysts with hyperplasia of the internal theca, but no signs of activity in the granulose.

Insulin resistance is prevalent in 30%–40% of cases and PCOS has been associated with hypertension, reduced vascular compliance, coronary microvascular disease, strokes, and dyslipidemia. Women with PCOS are at increased risk for developing type 2 diabetes [44].

The most frequent cutaneous sign is hirsutism [55] that has been observed in 40%–92% of European and American women [2] although it is also possible to find acne that tends to persist until the menopause [52], oily skin, androgenetic alopecia, obesity and, less frequently, seborrheic dermatitis and acanthosis nigricans. Hirsutism, which is the second most common sign of PCOS after oligomenorrhea, localizes usually on the lateral surfaces, especially on the breast (Fig. 17.7),



Fig. 17.7 Stein-Leventhal syndrome with hirsutism (Ferriman and Gallwey score 4) on the abdomen

lateral areas of the face and neck, and also on the abdomen. PCOS is also prevalent in women with late-onset acne, persistent acne, and acne resistant to conventional therapies.

Excess of weight and obesity are common in PCOS, being demonstrated in 30%–75% of women. The distribution of adiposity is critical, with abdominal obesity associated with increased risk of insulin resistance, cardiovascular disease, breast and uterine cancer, and sleep apnea [52]. Weight can be assessed using the body mass index (BMI) considering a normal weight as a BMI of about 19–25 kg/m², being overweight as a BMI of 26–29 kg/m², obese as a BMI of 30–37 kg/m², and morbidly obese as a BMI ≥37 kg/m². A subcutaneous fat pattern relates to fertility, a gynoid fat pattern is a sign of potential fertility, whereas an android fat pattern is associated with decreased fertility [44, 52].

Biochemical tests show that the serum total testosterone, free testosterone, Δ-4-androstenedione, and estrone levels tend to increase. Levels of SHBG are decreased, and this is more evident in obesity [28, 38, 39]. Levels of LH will be increased and the LH:FSH ratio will also be increased in up to 95% of women with PCOS. Sometimes, DHEA-S is increased, via an unknown mechanism, and serum prolactin levels are also increased. All cases of PCOS with severe hirsutism have increased serum PSA levels [16, 39]. Fasting insulin, fasting glucose, and oral glucose tolerance test are recommended in obese women [52]. It is also possible to demonstrate elevated serum triglycerides and total cholesterol, and low HDLs.

HAIRAN syndrome is a severe variant of PCOS that received its name from the acronym of its three principal symptoms: *h*yperandrogenism, *i*nsulin *r*esistance and *a*canthosis *n*igricans [18]. There are two types: type A, which is inherited with severe insulin resistance from insulin receptor mutations; and type B, which is less severe and is an autoimmune acquired condition resulting from antibodies to the insulin receptor. HAIRAN syndrome is also associated with other autoimmune endocrinopathies such as Hashimoto's thyroiditis, Graves' disease, CAH, and Cushing syndrome. HAIRAN syndrome is advanced evolution from HAIRAN SAHA or "familial virilization" [65]. The pathogenesis of this syndrome is the same as classic ovarian hyperandrogenism, and women suffering from either syndrome tend to be hyperinsulinemic and obese. Hyperinsulinemia is a consequence of the effect of insulin resistance on the insulin and insulin-like growth factor-1 (ILGF-1) receptors. These receptors are in the ovary and it has been demonstrated that ILGF-1 directly stimulates the production of androgens by ovaric theca cells and reduces hepatic production of SHBG, with the woman indirectly reaching a hyperandrogenic status in relation to the high levels of free testosterone [16]. Laboratory tests show increased serum levels of insulin, testosterone, and Δ-4-androstenedione. Positive ANA and elevated erythrocyte sedimentation rate are sensitive for the type 2 HAIRAN variant of PCOS.

17.4.3.1.2 Ovarian Hyperthecosis

Ovarian hyperthecosis is similar to Stein–Leventhal syndrome, but with greater production of androgens, especially testosterone. The patients present with signs of virilization, with hirsutism, and even androgenetic alopecia of a male pattern. Serum levels of LH and FSH are normal, but estrone levels are greatly elevated [7, 38].

17.4.3.2 Tumoral Ovarian Hirsutism

If the hirsutism is mild and there is relative virilization in an older woman, even post-menopausally, one should think about the possibility of an ovarian tumor. Arrhenoblastomas, hilus cell tumors, granulosa cell tumors, Brenner's tumors, and gonadoblastomas can cause tumoral ovarian hirsutism. In the exceptional case of a hilus cell tumor secreting exclusively estrogens, obviously there is no virilization [14]. Luteoma or pseudotumoral thecomatosis is a "physiological pseudotumor" which develops in 1 of every 400 pregnancies due to stimulation of gonadotropins of placental origin. It affects the ovaries and causes a materno–fetal virilization syndrome, which disappears after birth [7].

17.4.4 Pituitary or Hypophyseal Hirsutism

This type of hirsutism is due to the secretion of hormones from the anterior pituitary, in particular prolactin. There are a number of etiologies of hyperprolactinemia, although pituitary adenomas and drugs are the major causes. Clinical features are "amenorrhea–galactorrhea syndrome" and infertility. Generally women younger than 50 years of age, who are usually introverted and very nervous, present with FAGA, acne, seborrhea, and hirsutism, both central and lateral, although with a slight predominance of the former. There are signs of virilization, and galactorrhea is present in 30%–80% of the patients. Amenorrhea is also present in 70% of the cases and, conversely, 15%–25% of amenorrheic (but not pregnant) women have hyperprolactinemia. Biochemical investigations will show, above all, an increase in prolactin [38]. PSA levels may also be increased, especially when acromegaly is present [54].

17.4.5 Hepatic Hirsutism

This is a type of hirsutism related to a decrease in SHBG. It must be made clear that hirsutism does not occur by this mechanism alone, but rather the decrease of SHBG is a factor that usually accompanies hirsutism secondary to dysfunction of the adrenals glands or the ovaries [38]. Laboratory tests will demonstrate high serum levels of free testosterone and 5-α-DHT [7, 14].

17.4.6 Iatrogenic Hirsutism

This type of hirsutism tends to be localized on the lateral aspects of the face and back. Anabolic steroids (e.g., danazol), oral contraceptives of the nonsteroidal progestogen type, and other drugs such as minoxidil, ciclosporin, diphenylhydantoin, and glucocorticosteroids have been reported to cause hirsutism. There are no laboratory abnormalities. When the drug is discontinued, the hirsutism tends to disappear [7, 14].

17.4.7 Hirsutism due to Ectopic Hormones

Hirsutism may be associated with carcinoid tumor, choriocarcinoma, and metastatic lung carcinoma. Patients develop a central or lateral hirsutism depending on the hormone produced by the tumor. Carcinoid tumor and metastatic lung carcinoma cause an increase in cortisol and consequently a Cushingoid syndrome. Choriocarcinoma causes secondary hyperthyroidism [7, 14].

17.4.8 Hirsutism due to the Alteration of the Peripheral Conversion of Androgens to Estrogens

This is a hypothetical cause of hirsutism. Even if a woman were to lack ovaries, the conversion of androgens to estrogens would take place in the adipose tissue and in the liver [55], although, logically, this would take place in smaller amounts [7, 14].

17.5 Diagnosis of Hirsutism

When we are consulted by a patient with hirsutism, the first step in their evaluation is to determine the source of the responsible androgens, i.e., adrenal cortex or the ovaries. The marker for adrenal gland androgens is DHEA-S, and the marker for androgens produced in the ovaries is Δ-4-androstenedione. 5-α-DHT is the androgen responsible for androgenetic alopecia and hirsutism via interaction with 5-α-reductase type 2 isomerase, whereas type 1 is responsible for the development of acne [26].

It should be noted that as a general rule "*whenever there is hirsutism which appears abruptly and which evolves quickly, one must first suspect that there is an ovarian, adrenal or pituitary tumor.*" In addition, when the hirsutism is mainly localized to the areola and the lateral surfaces of the face and neck, the androgens usually have an ovarian origin, whereas if the location is central, with a distribution from the pubic triangle to the upper abdominal area, between the breasts, to the neck and the chin, the origin is usually adrenal [9]. When there is only hair on the lateral aspect of the face and on the back, the hirsutism is usually iatrogenic. With time, however, the distribution can evolve to produce both central and lateral involvement.

The degree of hirsutism is quantified by the Ferriman and Gallwey scoring system [34]. Nine regions are assessed (see Chap. 8) to give a score of 0 (no terminal hair) to 4 (extensive terminal hair). Functional hirsutism is generally defined as a score greater than 8; an organic hirsutism, a score greater than 15. We also use the Abraham's classification [7, 14] (Table 17.1).

We use an algorithm (Fig. 17.8) to obtain different diagnostic possibilities. Initially we begin with a detailed history looking for any clinical signs, which may orientate our initial diagnosis (a clinical impression of acromegaly, Cushing's features, physical virilization, menstrual alterations, infertility, hypertension, galactorrhea, etc.), and then start the laboratory evaluation.

In our protocol, we consider it essential to request levels of testosterone, free testosterone, 5-α-DHT, DHEA-S, 17-β-hydroxyprogesterone, prolactin, Δ-4-androstenedione, SHBG, and 3-α-androstanediol glucuronide, a metabolite of 5-α-DHT. Knowing that PSA is a marker of androgenization [30, 60] in both premenopausal (normal levels $\leq$ 0.02 ng/ml) and postmenopausal women (normal levels $\leq$0.04 ng/ml), we introduced this antigen into our protocols in 2001 [19, 66].

Table 17.1 Abraham's classification. Based on the Ferriman and Gallwey score

Score	Presentation
<8	Normal
8–16	Discrete hirsutism
17–25	Moderate hirsutism
>25	Significant hirsutism

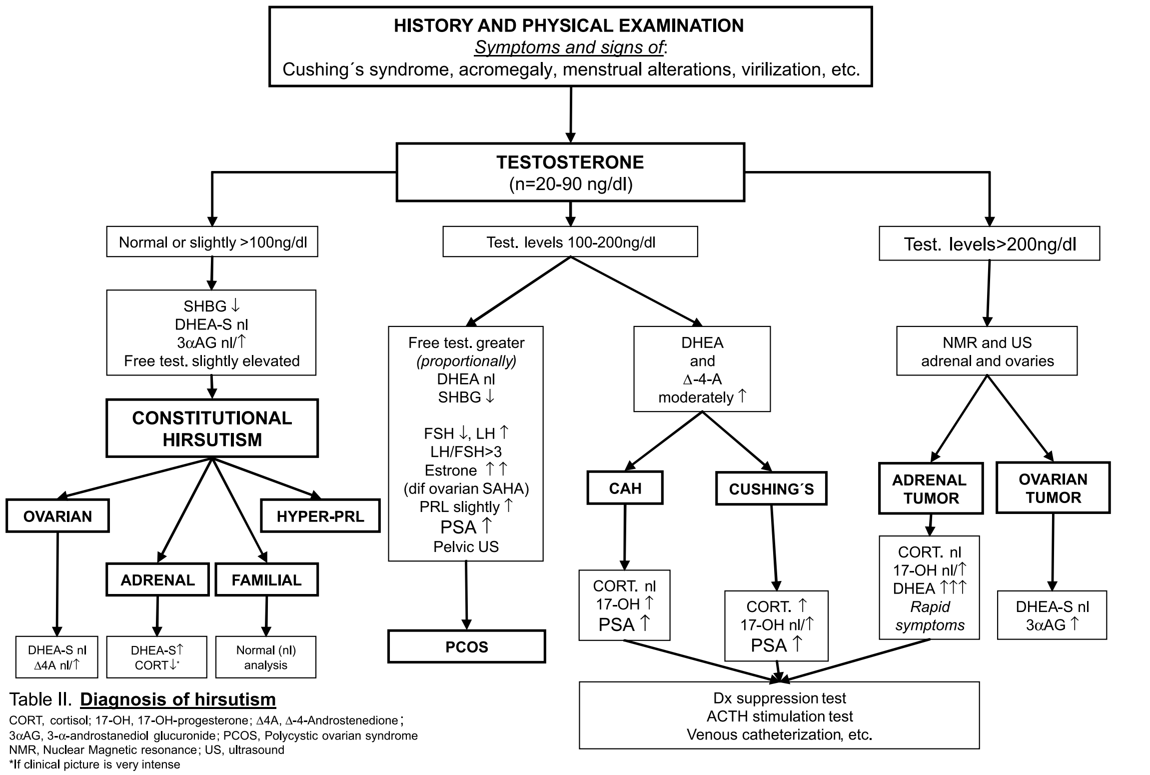


Fig. 17.8 Algorithm for diagnosis of hirsutism. (*17-OH* 17-OH Progesterone, *Δ4A* Δ4-androstenedione, *3αAG* 3-α-androstanediol glucuronide, *ACTH* adrenocorticotropic hormone, *CORT* cortisol, *DHEA-S* dehydroepiandrosterone sulfate, *Dx* dexamethasone, *NMR* nuclear magnetic resonance, *PCOS* polycystic ovary syndrome, *PRL* prolactinemia, *PSA* prostate-specific antigen, *SHBG* sex hormone binding globulin, *US* ultrasound.) *If clinical picture is very intense

Cortisol levels will be normal in CAH and adrenal tumors, and increased in Cushing syndrome [58]. If CAH is a possibility, the levels of 17-hydroxyprogesterone before and after an "*ACTH stimulation test*" may be investigated. When, 1 h after the administration of 250 mg synthetic ACTH, a massive increase of 17-hydroxyprogesterone is observed, a diagnosis of 21-hydroxylase deficiency will be assured [58]. When cutaneous signs of Cushing's syndrome are present, 24-h urinary free cortisol and creatinine excretion must be determined [58], and the overnight "*dexamethasone (Dx) suppression test*" can also be performed. With this test we can observe: (1) CAH: the Dx test causes a previously increased 17-hydroxyprogesterone level and a previously normal cortisol level to decrease; (2) Cushing syndrome: the Dx test does not change a previously normal or slightly increased 17-hydroxyprogesterone level, or a previously increased cortisol level; (3) adrenal tumors: 17-hydroxyprogesterone that was also normal or slightly increased does not change after a Dx test, and cortisol that was normal decreases after the Dx test [58].

Gonadotropins LH, FSH and the LH:FSH ratio must be determined to confirm PCOS because an elevation in serum LH is pathognomic of, but not required for, a diagnosis of PCOS, and ratio LH:FSH ≥3 can be elevated in up to 95% of subjects [52]. Given the prevalence of impaired glucose tolerance in PCOS, and its consequent morbidity, all women with PCOS must be screened for type 2 diabetes mellitus [11]. Serum triglycerides, total cholesterol, and HDLs must be also screened because dyslipidemia is predictive of associated cardiac morbidity. When HAIRAN syndrome is suspected insulin serum levels must also be determined [7, 12]. When evaluating PCOS patients, ultrasound examination of the ovaries should be performed, and as these patients usually carry excess weight obesity can be assessed using the BMI; also the "waist-to-hip ratio" must be evaluated to determine the fat distribution. In cases of clear obesity, transvaginal ultrasound must be made [52]. When tumors are suspected magnetic resonance imaging (MRI) and ultrasound may be neccesary.

17.6 Treatment of Hirsutism

The principal types of constitutional hirsutism of the SAHA syndrome must be treated in a similar way to ovarian, adrenal or pituitary organ failure, although naturally the dose will be lower and the treatment shorter in duration. Nevertheless, when patients also present with other symptoms of virilization that would lead us to a diagnosis of completely constituted ovarian, adrenal or pituitary hyperandrogenism, the dermatologist should refer the woman to the corresponding specialist, e.g., endocrinologist or gynecologist, without delay [7, 11, 13, 33].

The dermatological treatment of hirsutism is discussed separately as systemic, topical and dermato-cosmetic therapies.

17.6.1 Systemic Treatment

17.6.1.1 Constitutional, Adrenal, Ovarian and Pituitary Hirsutism

17.6.1.1.1 Persistent Adrenarche Syndrome (Adrenal SAHA) and Adrenal Hyperandrogenism

Two types of drug must be used: corticosteroids to adrenal suppression and antiandrogens (central or peripheral), to avoid the production of adrenal androgens or their effects on the target follicular organ.

17.6.1.1.1.1 Adrenal Suppression

Adrenal suppression is achieved with glucocorticosteroids. Several years ago, we used dexamethasone at an initial dose of 0.5 mg every night for 3 months and then on alternate nights for a further 3 months. If the dexamethasone doses were greater than 0.75 mg daily and given for 6 months or more, we could observe Cushingoid changes [11]. Prednisone at a dose of 7.5 mg daily for 2 months, reduced to 5 mg daily (for 2 months) and then 2.5 mg daily, until 6 months of treatment is completed, is an alternative. At present we use deflazacort at an initial dose of 30 mg qd for 1 month with a maintenance dose of 6 mg daily for up to 2 years. Deflazacort has the advantage that, at this dose, it does not produce side-effects. These doses of glucocorticosteroids are enough to reduce the level of DHEA-S, Δ-4-androstenedione and testosterone [14]. The only secondary effect is that obese women, who are not the norm in adrenal SAHA, tend to gain a little more weight. Adrenal hyperplasia is treated with substitutive corticosteroid therapy, regardless of the enzyme deficiency. Cushing syndrome benefits from substitution therapy with corticosteroids plus surgery and/or irradiation [11].

17.6.1.1.1.2 Antiandrogen Therapy

Antiandrogen therapy includes cyproterone acetate, spironolactone, drospirenone, flutamide, finasteride, and dutasteride. Central antiandrogens competitively inhibit the binding of 5-α-DHT to the androgen receptor [52], and peripheral antiandrogens act by inhibiting 5-α-reductase, blocking the conversion of testosterone to 5-α-DHT [15].

17.6.1.1.1.2.1 Antagonists of Androgen Receptors

Cyproterone acetate (CA) acts by interfering with the binding of 5-α-DHT to the androgen receptor and by inhibiting the secretion of FSH and LH through its progestogen action. The recommended dose is 50–100 mg/day from the 5th to the 15th days of the menstrual cycle for a 6-month period, which is the time of glucocorticosteroid suppression. When the maintenance of treatment is necessary, 2 mg/day from the first day of the cycle to the 21st day with a week of rest may be given. As CA usually causes feminization in the male fetus, as well as menstrual alterations, even at doses of 50 mg a day, it is best to add oral contraceptive pills (OCPs) such as ethinyl estradiol. In postmenopausal women with slight hirsutism, generally on the face, cyproterone acetate can be administered in doses of 50 mg a day without interruption [11]. Side-effects include loss of libido, mood swings, fatigue, mastodynia, hypertension, and weight gain. It is absolutely contraindicated in patients with liver disease. In my opinion, CA is the best treatment for the alopecia of SAHA syndrome [15] but it has less effect in the treatment of hirsutism in SAHA and adrenal hirsutism [11].

Spironolactone is an aldosterone antagonist that also has antiandrogen activity, decreasing the levels of total testosterone. It is used at a dose of 50–200 mg/day for at least 6 months [20], starting at a low dose of 50 mg/day, which is enough in adrenal SAHA, and increasing monthly the dose up by 50 mg to a final dose of 200 mg/day. This dose reduces the diameter of facial vellus hair in 83% with CAH after 12 months [14]. Lethargy, upset stomach, and menorrhagia are common and transient side-effects, which tend to resolve spontaneously after 2 or 3 months of therapy. Nevertheless, to decrease the incidence of menorrhagia, low-dose OCP may be used [52]. Other potential side-effects include a decrease in libido, an increase in breast size, headache, and hyperkalemia [75]. Although the risk of hyperkalemia is very

low in healthy young women, some authors advise patients against excessive intake of bananas and diet soda, and periodically study the serum potassium levels. Spironolactone is synergistic when used in combination with OCPs in the treatment of facial hirsutism to prevent testicular feminization of an exposed fetus. This drug is category X for pregnancy [52]. Cutaneous side-effects as pruritus, xerosis, maculopapulous eruptions, urticaria, facial-pigmentations-type melasma, contact dermatitis, erythema annulare centrifugum, vasculitis, erythema multiforme, Raynaud's phenomenon, alopecia, lupus type eruption [11, 40], and, on two occasions, a lichenoid eruption [73] have been described.

Drospirenone is a 17-α-spironolactone derivative with progestagenic, antiandrogenic and antialdosteronic activities. Doses of 3 mg/day over 21-day cycle along with 30 µg ethinyl estradiol is currently the normal choice in the treatment of SAHA, particularly because drospirenone does not cause fluid retention and consequently the patient does not gain weight [15]. Its efficacy in the treatment of CAH and Cushing syndrome has not been demonstrated.

Flutamide is a pure, non-steroidal antiandrogen. It is used at a dose of 250–500 mg twice a day for 6–9 months for prostatic hyperplasia. At present this is considered to be the most effective antiandrogen for the treatment of adrenal SAHA or hirsutism in women with normal ovaries. In this case, low doses of 62.5–125 mg daily can be used [25, 29, 59] (Figs. 17.9, 17.10). Flutamide is also the best antiandrogen to use in the treatment of adrenal hirsutism, at a dose of 250–750 mg daily, although this dose has the risk of severe hepatotoxicity in 13% of patients, and their control every 3 months by means of functional tests is required. Other side-effects include lethargy, dry skin, mood change, and loss of libido. As it may also cause feminization of the male fetus, tricyclic contraceptives must be employed; not only because of the possible effects on the fetus but also because it has been shown that they act to reduce hirsutism and especially because they prevent the relapse back to hirsutism once the treatment with flutamide is stopped [11]. Photosensitivity in a male with prostate carcinoma treated with flutamide has been published [82], a complication which must be taken into consideration especially in young women who tend to abuse exposure to sunlight in summer.

Cimetidine is a H2 blocker that can also act as a peripheral antiandrogen by inhibiting the binding of 5-α-DHT to the androgenic receptor [11]. Some authors suggest that it could be used in SAHA at a dose of 300 mg five times a day, preferably in association with OCP, because it has demonstrable usefulness in the treatment of acne, with a similar effect to spironolactone [46]. A case of "fixed exanthema" has been reported with its use [48]. Nevertheless, we think that cimetidine has anecdotal value because its use causes an increase in androgen secretion through a negative feedback mechanism [11].

17.6.1.1.1.2.2 5-α-Reductase Inhibitors

There are two types of 5-α-reductase isoenzymes: type 1, reported to be found predominantly in sebaceous glands; and type 2, predominantly in the prostate and certain regions of terminal hairs. Approximately 70%–80% of serum 5-α-DHT is produced by the type 2 isoenzyme and 20%–30% by the type 1 isoenzyme [51]. As a consequence, when we write about specific 5-α-reductase inhibitors, we have to specify the type. Inhibitors of 5-α-reductase isoenzymes do not act purely against one or the other type; for example, finasteride is predominantly a 5-α-reductase type 2 inhibitor but it also has



Fig. 17.9 Adrenal SAHA before treatment



Fig. 17.10 Adrenal SAHA after 6 months of treatment with 125 mg/day flutamide and tricyclic contraceptive

activity against the sebaceous gland [15]. Currently, finasteride, dutasteride, and isotretinoin are available. Other antiandrogens of steroid configuration such as desoxycorticosterone, androstenedione, and progesterone, which act as 5-α-reductase inhibitors, have a limited use due to their systemic androgenic hormonal effects. New steroid 5-α-reductase inhibitors synthesized in the laboratory (dienones and trienones) inactivate the enzyme by an irreversible Michael-type addition of the nucleophilic portion of the enzyme to the conjugated double bond of the steroid [6, 35]. In the treatment of hirsutism, experience is limited to finasteride.

Finasteride is considered to be a potent non-steroidal antiandrogen that acts by inhibiting the type 2 5-α-reductase isoenzyme, blocking the conversion of testosterone to 5-α-DHT. When a dose of 5 mg/day, or 7.5 mg/day, for 3–6 months was used, a significant reduction of serum and follicular DHT levels was observed [36, 61]. In total, 89 patients with *persistent adrenarche syndrome* were treated with 2.5 mg daily for 2 years, achieving a 93% reduction of facial hirsutism and a 73% reduction of corporal hirsutism in 72 patients [13] (Figs. 17.11, 17.12), with a significant reduction of serum 5α-DHT levels and no prominent side-effects. Other authors, also treating with 2.5 mg/day finasteride, demonstrated that hirsutism was clearly reduced using the Ferriman and Gallwey score [23, 79]. Hirsute women with CAH or Cushing's syndrome could benefit from finasteride but as these authors are gynecologists it is reasonable to think that they were treating ovarian SAHA syndrome (which they name "idiopathic hirsutism") and PCOS. Although finasteride is well tolerated and safe, it does have some side-effects that are usually slight, especially in women. As this apparently causes feminization of the male fetus, OCPs must be added. It does not have any effect on serum lipids or on bone density, nor does it show any drug interactions; however, when used in association with OCPs, there is a marked increase in serum cholesterol levels [1]. It has also been shown that, in hirsute women, there is a slight increase in gonadotropins and testosterone.

Dutasteride is a potent non-steroidal antiandrogen that acts by inhibiting 5-α-reductase isoenzymes 1 and 2 in humans, lowering serum and scalp 5-α-DHT levels. There is no experience in the treatment of hirsutism, although recently several reports about using dutasteride in androgenetic alopecia in men [62] and women [63] were published. The patient with FAGA had been treated unsuccessfully with cyproterone acetate and ethinyl estradiol, but showed significant improvement after dutasteride treatment. In total, 25 postmenopausal women with female androgenetic alopecia of male pattern (FAGA.M) degree II–III Ebling (III–V Norwood/Hamilton) were treated with 0.25 mg/day of dutasteride, demonstrating an improvement in 60% at 1 year of treatment rising to 80% at 2 years [21], starting in the frontotemporal region followed by the vertex and frontal areas. In all cases serum 5-α-DHT and PSA levels were reduced. Recently 14 postmenopausal women with FAGA.M [16], and 5 women with FAGA.M (central hirsutism degree 9 and nodulo-cystic acne), corresponding to *persistent adrenarche syndrome*, were treated with a 0.5 mg daily dose of dutasteride and 2.5 mg/day finasteride for 6 months, achieving an improvement of alopecia in all cases, and of hirsutism and acne in 4 cases (80%). The aim of using this combination is to obtain a 100% re-



Fig. 17.11 Adrenal SAHA syndrome before treatment



Fig. 17.12 Adrenal SAHA syndrome after 2 years of treatment with finasteride 2.5 mg/day

duction of 5-α-reductase, and consequently of 5-α-DHT, alopecia, central hirsutism and seborrhea-acne, similar to the reduction in 5-α-DHT serum levels observed using TrichoScan, Ferriman and Gallwey score and sebumeter at baseline, 3 and 6 months. Although dutasteride seems to have fewer side-effects than finasteride [62], OCPs must be co-prescribed because dutasteride, like all antiandrogens, can feminize a male fetus.

Isotretinoin: although this does not appear to have a significant effect on circulating androgen levels, it has been shown to decrease the activity of 5-α-reductase and thus the production of 5-α-DHT and its metabolites [11]. We have never used isotretinoin to treat constitutional hirsutism; nevertheless, when we used it for nodulo-cystic acne we could see that the seborrhea was reduced in a similar manner to the reduction observed with flutamide and dutasteride.

17.6.1.1.2 Excess Release of Ovarian Androgens (Ovarian SAHA) and Ovarian Hyperandrogenism

Three types of treatment must be used: contraceptives for ovarian suppression, gonadotropin-releasing hormone agonists (GnRH-a) for pituitary and gonadal suppression, and antiandrogens. Endocrinologists and/or gynecologists can use other treatments for insulin resistance or to restore ovulation, logically independently of hirsutism.

17.6.1.1.2.1 Ovarian Suppression

Ovarian suppression with oral contraceptive pills (OCP) is the first-line therapy for hirsutism and acne in women with ovarian SAHA syndrome and PCOS [52]. The choice of OCP is important because this contain an estrogen, ethinyl estradiol (EE), and a progestin. The estrogenic component suppresses LH and ovarian androgen production, and enhances SHBG production in the liver, thus reducing free testosterone and as a consequence 5-α-DHT [14]. Estrogens can also decrease sebum production but at doses higher than those used for oral contraception [52]. Difficulties in the election of the OCP are caused by progestins, because some are pro-androgenic and some antiandrogenic in their effect. Thus, the least androgenic progestins are norgestimate and desogestrel, whereas the most androgenic progestins are norgestrel and levonorgestrel. As a consequence, the combination of EE with norgestrel, and/or levonorgestrel should be avoided, and the association of EE with norgestimate or desogestrel recommended. These should not be used in women with insulin resistance, thrombophlebitis, cerebrovascular disease, coronary occlusion, abnormal vaginal bleeding, impaired liver function, migraine, in smokers older than 35 years, and in individuals at increased risk of breast cancer [11, 52]. Transdermal delivery of contraceptives is now available and can avoid liver metabolism and decrease the risk associated with OCPs.

If the patient does not tolerate OCP, one can use medroxyprogesterone acetate at 5 mg daily or twice a day; it is a synthetic progesterone that is used as an anovulatory agent because it inhibits gonadotropin secretion, especially LH, which reduces the production of testosterone and Δ-4-androstenedione in the ovaries [11]. In women older than 40 years, the administration of 4 mg of estradiol valerate (EV) orally may be used instead of EE, and, in the case of an oral intolerance of estrogens, one can administer 10 mg EV i.m. on days 5 and 15 of the cycle [11, 41].

17.6.1.1.2.2 Gonadotropin-Releasing Hormone Agonists (GnRH-a)

Although their use in SAHA syndrome is not usually considered, they are useful in the treatment of hirsutism, acne, and seborrhea presented by severe forms of *ovarian hyperandrogenism* and especially in *HAIRAN syndrome*. As this treatment is expensive its use will be only justified in these severe forms [11].

GnRH agonists were introduced in 1971 to treat hirsutism as they decrease the diameter of the hair shaft, hair growth rates, and the Ferriman and Gallwey score. Their effects are due to continual stimulation of the pituitary thus reducing LH and FSH production, and the LH reduction in turn leads to a fall in ovarian steroids levels, Δ-4-androstenedione, testosterone and free testosterone, especially in patients with PCOS. Its use is limited because of its side-effects, which cause loss of bone matter as a result of estrogenic depletion. As a consequence, GnRH-a are currently administered in association with estrogens and progesterone, and these in turn increase the SHBG and also reduce the free testosterone.

Probably, the most useful GnRH-a in the treatment of hyperandrogenic women is *leuprolide*, which is at least more effective than standard OCP therapy alone. A dose of 20 µg/kg per day in combination with 2 mg EE and 5 mg medroxyprogesterone acetate for 6 months was an effective and well-tolerated treatment in women with hirsutism caused by PCOS [57].

Triptorelin is a long-acting GnRH agonist useful in the treatment of hirsutism. A comparative study between cyproterone acetate (CPA) 2 mg with 35 µg EE for 21 days each month (Diane group); CPA 50 mg, days 5–15, and EE 50 µg, days 5–25 each month (CPA

group); and triptorelin 3.75 mg i.m. every 28 days with the addition of conjugated estrogen 0.625 mg, days 1–21, and medroxyprogesterone acetate 10 mg, days 12–21 (GnRH-a group) was evaluated in a total of 60 hirsute hyperandrogenic women. All women were treated for 1 year with a 1-year follow-up [22]. After 1 year of treatment, hirsutism decreased in all three groups but the changes were greater in the CPA and GnRH-a groups. After withdrawal, hirsutism increased rapidly in the Diane and CPA groups and more gradually in the GnRH-a group. The conclusion of this study suggests equal efficacy of the GnRH agonist and the high-dose CPA regimen for the treatment of hirsutism [22]. However, another similar comparative study over 9 months between CPA (100 mg, days 1–10), triptorelin (3.75 mg i.m. every 28 days), and flutamide (250 mg twice a day), always with the addition of a tricyclic contraceptive with EE and levonorgestrel, demonstrated that hirsutism graded by the Ferriman and Gallwey score decreased in all groups although the changes were greater in the flutamide group and less evident in the triptorelin group in addition to its high cost and increased serum lipid levels [69].

Treatment of *HAIRAN syndrome* has focused on lowering insulin levels with a combination of weight loss, OCPs, antiandrogens, and a GnRH agonist known as *metformin*, which can be also effective in the treatment of PCOS [69], to improve the hirsutism [3]. Doses of metformin between 500 and 855 mg, three times daily, have been shown to have the following effects: doubling of the frequency of menses in those patients with oligomenorrhea in both dose groups; a modest improvement in markers of insulin resistance [43], most evident in the 2550 mg/day dose group; a marked reduction of circulating serum Δ-4-androstenedione levels, also most evident in the high-dose groups; no effect on circulating testosterone or SHBG; significant reductions in total cholesterol and LDL-C with no effect on circulating triglycerides or HDL in both groups; highly significant reductions in leptin levels in both groups that were not reflected by changes in circulating C-reactive protein; and a modest reduction in circulating LH in both groups in both dosages [44]. Changes in variables were examined with respect to weight change and the change in the glucose:insulin ratio correlated strongly with the weight loss [44, 49].

17.6.1.1.2.3 Antiandrogens

Antiandrogens used in the treatment of *ovarian SAHA* and *PCOS* are the same as those used to treat adrenal SAHA and adrenal hyperandrogenism. There is more experience with the latter because of the greater incidence of ovarian diseases associated with hirsutism and gynecologists use this therapy to treat them.

We have experience using *cyproterone acetate* at a dose of 100 mg/day [11], *flutamide* at a dose of 125–500 mg/day [55], and *finasteride* at a dose of 2.5–5 mg/day [13] , always accompanied by OCPs; we obtain a significant reduction of hirsutism with flutamide and finasteride, greater than with cyproterone acetate.

For many years our therapeutic standard consisted of administering, for a period of 6 months, 100 mg/day *cyproterone acetate* from the 5th to the 15th day of the menstrual cycle, and 35 µg EE from the 5th to the 26th day of the cycle. For a further 18 months the patient would take 2 mg cyproterone acetate and 35 µg EE from the 5th to the 26th post-menstruation days. It should be pointed out that this last combination is only effective in mild *ovarian SAHA*, and as a maintenance therapy; it has no use as primary therapy in the first 6 months. After 2 years we would repeat the biochemical test, as some patients required treatment for 3 years or more. Equal efficacy of the GnRH agonist and high-dose cyproterone acetate for the treatment of hirsutism has been suggested [22].

Since 1995 we have used 67.5 mg/day *flutamide* to treat *ovarian SAHA* and 125–250 mg/daily to treat *PCOS*. We changed the antiandrogen on the basis of a study in which we compared the response of hirsutism in PCOS in two groups of women, one group (n=17) treated with cyproterone acetate 100 mg daily and the other (n=14) with flutamide 250 mg/day [55]. After 6 months, the hirsutism score of the flutamide group had reduced significantly more than the score of the cyproterone acetate group (50.6±16.7 vs. 34.0±8.0; p<0.001) with similar reductions of serum LH, FSH, Δ-4-androstenedione, prolactin, DHEA-S, and testosterone levels. Similar results have been obtained by other authors comparing triptorelin (3.75 mg i.m.), flutamide (500 mg/day), and cyproterone acetate (100 mg/day), used in combination with OCP [69]. Flutamide (250 mg/day) is also effective in the treatment of *SAHA type HAIRAN syndrome*, decreasing the serum insulin level [67], and in the treatment of adolescent, non-obese girls with oligomenorrhea, improving their dyslipidemia and hyperinsulinemia [47].

For the last 7 years (2000–2007) we have treated *ovarian SAHA* with *finasteride* 2.5 mg/day and *PCOS* with 5 mg/day, always controlled by the serum 5α-DHT and PSA levels [13, 14, 15, 16]. We treated 41 hirsute women with nodulo-cystic acne (*34* diagnosed with *ovarian SAHA syndrome* and *7* with *SAHA type HAIRAN syndrome*) with 2.5 mg finasteride daily for 2 years; overall the hirsutism score decreased from a mean of 17.4±4.4 to 8.3±3.9, there was an improvement of 96% in acne (Figs. 17.13, 17.14) and significant decrease in the serum



Fig. 17.13 SAHA type HAIRAN syndrome before treatment. Lateral facial hirsutism and nodulo-cystic acne



Fig. 17.14 SAHA type HAIRAN after 2 years of treatment with finasteride 2.5 mg/day

levels of free testosterone, 5-α-DHT, 3-α-androstanediol glucuronide and *PSA* [15]. Our results are similar to different studies of Italian gynecological schools using 2.5 mg/day [4, 31, 32], 5 mg/day [79], or 2.5 mg every 3 days [78].

Comparative studies in 40 hirsute women with *ovarian SAHA* syndrome and *PCOS* with the three antiandrogens available in the USA [15, 56], namely *spironolactone* (100 mg/day), *flutamide* (250 mg/day), and *finasteride* (5 mg/day), demonstrated similar effects, decreasing hirsutism according to the Ferriman and Gallwey score and the diameter of a middle abdominal hair shaft. Another study investigated 2 groups of 25 women, 15 with *constitutional hirsutism* and 10 with *PCOS*. They were treated with *finasteride* 5 mg or placebo during the first 14 days of menstrual cycle, but both groups also took cyproterone acetate 2 mg and EE 35 μg. The response was better in the group that received finasteride, and in conclusion the authors recommended finasteride as the first-line treatment of hirsutism at least in constitutional hirsutism [77].

17

17.6.1.1.2.4 Endocrinological or Gynecological PCOS Treatment

Endocrinologists treat dyslipidemia and hyperinsulinemia, while gynecologists restore ovulation/fertility. Dyslipidemia is treated with statins plus OCP, leading to significantly lowered testosterone levels and normalized gonadotropin levels, with no effect on hirsutism [77]. Insulin resistance is treated with metformin and two *thiazolidinediones* (*rosiglitazone* and *pioglitazone*) that have demonstrated improvements in insulin resistance, hyperandrogenemia, and glucose tolerance. Using these *thiazolidinediones*, ovulation was significantly increased, free testosterone levels decreased, and SHBG levels increased [50]. Thus, insulin-sensitizing agents are the subject of continued research on improving ovulation, as well as improving the cardiovascular risk factors associated with hyperandrogenemia in PCOS. To increase ovulation in PCOS, clomiphene citrate, alone or with metformin, is useful. Newer ovulation-induction agents include the aromatase inhibitor *letrozole*, which, by decreasing estrogen production, leads to an increase of FSH and consequently to ovulation and delivery [5, 50]. Logically, in relation to its mechanism of action, letrozole can produce hair thinning.

17.6.1.1.3 Hyperprolactinemic SAHA and Pituitary Hyperandrogenism

These patients should be treated by a gynecologist with endocrinological expertise or an endocrinologist. However, when the predominant clinical picture is dermato-

logical, 2.5 mg/day of *bromocriptine* may be prescribed. Nevertheless it is convenient to remember that PCOS with hyperprolactinemia may be treated with clomiphene citrate to restore ovulation. *Cabergoline* is also used in the treatment of hyperprolactinemic hirsutism with the advantage that it is only used 1 day a week and at a dose of 0.5 mg [15, 24]. Side-effects include fatigue, lethargy, hypotension, depression, vomiting, and abdominal pain.

17.6.1.2 Iatrogenic Hirsutism

The responsible drug must be eliminated, and occasionally, dermato-cosmetic methods will have to be used.

17.6.1.3 Other Types of Hirsutism

It is exceptional to find hirsutism of hepatic origin, hirsutism of ectopic hormonal hyperproduction or hirsutism due to peripheral failure to convert androgens to estrogens. The treatment hereof needs to be carried out by a specialist, who would diagnose the main cause of the hyperandrogenism.

17.6.2 Topical Therapy

17.6.2.1 Familial Hirsutism

When we diagnose a familial SAHA syndrome with minimal clinical and with normal hormonal levels, we must use only local treatment and dermato-cosmetic treatment. Since 1980, we have been using 3% topical spironolactone and its metabolite canrenone at 1%–2%, with acceptable results in the treatment of hirsutism in SAHA [15].

17.6.2.2 Hirsutism of SAHA Syndromes and Hyperandrogenisms

We also use topical spironolactone or canrenone. Recently, the ornithine decarboxylase inhibitor eflornithine 11.5%–15% cream, in a twice-daily scheme of application, has been considered as a suitable alternative for facial hirsutism. Safety and effectiveness were demonstrated in double-blind studies [5, 15, 18, 52, 64, 81].

17.6.3 Dermato-Cosmetical Therapy

17.6.3.1 Chemical and Physical Depilation

There are many therapeutic options in this category, all of which have advantages and disadvantages [11, 14]. *Hair bleaching* is a popular practice, which may be carried out with 6% hydrogen peroxide, or with a 20% ammonia solution. *Shaving*, *depilation with tweezers,* and *wax depilation* are also common maneuvers. *Depilation with chemical substances*, such as 2%–4% calcium thioglycolate, allows for a longer interval between successive treatments. *Electrolysis* is the second most popular method at present, second only to laser treatment. To perform this technique it is necessary to have a machine that produces a galvanic current (galvanic electrolysis), and a high-frequency alternating current (thermolysis). This method of electrolysis is called "blend" and it is the one used at present [5, 11, 71]. The galvanic current produces sodium hydroxide which destroys the bulb, including the papilla, but this is a slow method which requires a minute or more on each hair. In contrast, thermolysis is a quick method which produces heat to destroy the hair in a few seconds. This heat destroys the vellus hair but thick hairs are more problematic, making combined use of the two methods necessary.

17.6.3.1.1 Laser and Intense Pulsed Light Sources

In theory, lasers and intense pulsed light sources (IPLs) are methods of "definite depilation." Alexandrite, Nd:YAG and diode [5, 17] are types of lasers used for this purpose. As these procedures are explained in Chap16, I will only mention here that the combination of eflornithine cream and laser hair removal results in a more rapid and complete reduction of unwanted facial hair in women when used for up to 6 months [42].

17.6.3.1.2 Lifestyle

Weight loss of only 2%–7% has been show to improve manifestiations of hyperandrogenism, including hirsutism [68], decrease hyperinsulinemia, and restore ovulation and fertility in up to 75% of obese women. Therefore, healthy eating, regular exercise, and weight reduction are encouraged [52]. However, there is no evidence that any particular diet regimen is more beneficial over another for obese women [50]. Adjuntive therapy with apetite suppressants, lipid antiabsorptive drugs, gastric stapling, and banding in obese patients may be of value [52].

Summary for the Clinician

Hirsutism is related to hormonal factors, mainly an increase in androgen levels. In females, the main sources of androgens with the capacity to produce hirsutism are the adrenal glands (dehydroepiandrosterone sulfate; DHEA-S) and the ovaries (Δ-4-androstenedione); however, the pituitary (prolactin) and the liver (SHBG) can also be responsible for some types of hirsutism. Ectopic hormones released by some tumors, certain drugs, and peripheral failure to convert androgens into estrogens may also cause hirsutism. If minimal or no hormonal abnormalities are found, the patient must be diagnosed as having a constitutional hirsutism (SAHA syndrome) or a familial hirsutism. The Ferriman and Gallwey score reflects functional hirsutism when the score is greater than 8, and an organic hirsutism when the score is greater than 15. Correct biochemical evaluation requires measurement of serum levels of free testosterone, 5α-DHT, DHEA-S, 17-β-hydroxyprogesterone, Δ-4-androstenedione, prolactin, SHBG, 3-α-androstanediol glucuronide and PSA. In cases of ovarian hirsutism the biochemical evaluation of LH, the LH:FSH ratio, FSH, and insulin levels is necessary. Depending on the origin of the hirsutism, the treatment is based on antiandrogens, glucocorticosteroids, gonadotropin releasing hormone agonists, and contraceptives, in association with topical and dermato-cosmetic therapies.

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Chapter 18

Scalp Tumors

Antonella Tosti, Massimiliano Pazzaglia, Bianca Maria Piraccini

18

Synonyms

skin cancer of the scalp, hair follicle associated tumors

Key Features

- Approximately 2% of all skin tumors are located on the scalp.
- Frequency increases with ageing.
- Malignant tumors are rare.
- Scalp tumors can be primary skin tumors or secondary, metastatic manifestation of other tumors.

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18.1 Introduction

Scalp tumors are skin cancers that can derive directly from the hair follicle epithelium, from the interfollicular epidermis or from other cell types. Thus, scalp tumors can be classified as tumors arising from the pilosebaceous unit with a differentiation pattern that depends on the cell population from which they originated (sebaceous, endothelial, epithelial, pigmented cells, fibroblasts, etc.), as tumors arising from the interfollicular epidermis or dermis or as metastases from other tumors.

Skin cancer of the scalp occurs most often in balding and elderly men who have had intense sun exposure, but they can also occur in humans with a full head of hair or rarely also in genodermatoses.

Rarely, other types of cancer can metastatize to the scalp and early detection is the key to successful management. The following most frequent scalp tumors can be distinguished: sebaceous nevi, actinic keratoses, basal cell carcinoma, squamous cell carcinoma, melanoma, angiosarcoma, scalp metastases or metastatic carcinoma of the scalp. Lymphoma or hemangioma can also be present on the scalp.

18.2 Tumors of the Pilosebaceous Unit on the Scalp [22]

Tumors of the pilosebaceous unit on the scalp are rare, and have nonspecific clinical aspects, the most common being trichoepithelioma and pilomatrixoma.

18

18.2.1 Trichoepithelioma

Synonyms
Brooke–Spiegler syndrome

Key Features

- Benign adnexal.
- 50% on scalp and face.
- May be isolated but most frequently occur in multiples.

Trichoepithelioma (TE) is a benign adnexal neoplasm that typically occurs in young to aging adults. The gene involved in the familial form of TE is located on band 9p21. Other cases are associated with Brooke–Spiegler syndrome (BSS) caused by mutations of the cylindromatosis oncogene (*CYLD*), which maps to 16q12-q13.

Clinically, TE appears as slow-growing, skin-colored single or multiple papules or nodules, 2–8 mm in diameter, usually on the face. Most lesions show slow growth.

18.2.1.1 Treatment Options

The treatment of TE is primarily surgical.

18.2.2 Pilomatrixoma

Synonyms
calcifying epithelioma of Malherbe, Malherbe epithelioma, trichomatrioma, benign calcifying epithelioma, hair cell tumor, Malherbe tumor, pilomatrix epithelioma, pilomatrix tumor, pilomatrical neoplasm, pilomatrix carcinoma, myotonic dystrophy, hair matrix cell tumorigenesis, hair matrix cell tumor, trichoadenoma

Key Features

- Benign adnexal tumors originating from hair matrix cells.
- Frequently occur in children.
- May be associated with syndromes.

A pilomatrixoma is a benign appendageal tumor with differentiation toward hair cells, common in children, usually becoming evident in the first 2 years of life. Pilomatrixoma usually manifests as a solitary, asymptomatic, firm nodule in the head and neck, especially the cheek, preauricular area, eyelids, forehead, scalp, and lateral and posterior neck. In ~3% of children pilomatrixoma occur in a multiple manifestation. It is important to know that these multiple pilomatrixoma can be associated with different syndromes: myotonic dystrophy Curschmann-Steinert, Gardner Syndrome, Rubinstein–Taybi syndrome, sarcoidosis, Turner syndrome, and Cleidocranial dysostosis.

18.2.2.1 Treatment Options

Spontaneous regression has never been observed. The treatment of choice is surgical excision. If the clinical diagnosis is not clear, fine needle aspiration cytology can

be performed. Patients should be monitored to ensure lesions do not recur after surgical excision.

18.3 Sebaceous Nevus

Synonyms
nevus sebaceous of Jadassohn, organoid nevus, verrucous epidermal nevi, epidermal nevus syndrome, Jadassohn nevus phakomatosis

Key Features

- Congenital hamartoma.
- Alopecic patch in children.
- Verrucous patch after puberty.
- Possible development of tumors.
- When follow Blaschko's lines may be a sign of neurocutaneous syndromes, Schimmelpenning Feuerstein Mims syndrome.

Sebaceous nevi are common, presenting in 0.8% of dermatological patients. They are found in about 0.3% of newborns and are usually diagnosed before the age of 40 years [17].

In children, sebaceous nevi present as a yellow or orange alopecic patch that frequently has a velvet surface. The patch usually enlarges and thickens at puberty, when it appears as a verrucous lesion without hairs (Fig. 18.1). When following Blaschko's lines, it must be considered whether the sebaceous nevi manifestation is a sign of a neurocutaneous syndrome (linear sebaceous nevus/Jadassohn nevus phakomatosis/Schimmelpenning Feuerstein Mims syndrome) (Table 18.1), which occur in 9.5% of cases with sebaceous nevi.



Fig. 18.1 Sebaceous nevus of the scalp: verrucous lesion devoid of hair

Table 18.1 Conditions that may be associated with linear sebaceous nevus [13]. (Schimmelpenning Feuerstein Mims syndrome)

Condition	Occurrence (% of patients)
Epilepsy	75
Mental retardation	70
Neurological defects (cranial nerve paresis, hemiparesis, cortical blindness)	50

Various adnexal tumors can develop in association with a nevus sebaceous, the most common tumor being syringocystadenoma papilliferum. The incidence of malignant tumors, particularly basal cell carcinoma, is low (0.8%–3.5%), always occurring after the third to fourth decade. Prophylactic surgical removal was widely recommended in the past but is not necessary. It is advisable to excise lesions that become more verrucous or enlarge or when associated tumors occur [13].

18.4 Actinic Keratosis

Synonyms
senile keratosis, solar keratosis, carcinoma in situ

Key Features

- Premalignant lesion.
- Common on the bald scalp of the elderly.

Actinic keratoses are common precancerous lesions accounting for presentations in about 14% of dermatological patients.

The main cause of actinic keratoses in healthy individuals is the sun and therefore they are commonly observed on the bald scalp of elderly men.

The incidence of actinic keratosis is increased in transplant recipients with a mean occurrence of 38% 5 years after transplantation [16].

Actinic keratoses appear as slightly raised hyperkeratotic erythematous areas. The surrounding scalp is bald

and typically shows signs of sun damage with hypopigmentation and freckles. The presence of erosions and crusts suggests possible malignant degeneration.

The risk of actinic keratosis developing into squamous cell carcinoma is about 16% over 10 years.

18.4.1 Treatment Options

All treatment options are in the field of topical management, such as cryosurgery, excisional surgery, topical 5-fluoruracil, topical imiquimod, topical diclofenac, and photodynamic therapy.

Choice of treatment depends on the number and location of the lesions. Both 5% imiquimod cream and photodynamic therapy provide complete cure in more than two-thirds of patients, with good clinical outcomes, low recurrence rates, and enhanced cosmetic acceptability [6]. Imiquimod cream is, however, very expensive. Topical diclofenac induces a reduction in lesion size in most cases but clearance only in 10% of them.

18.5 Basal Cell Carcinoma

Synonyms
basal cell epithelioma, rodent ulcer

Key Features

- This semi-malignant tumor rarely occurs on the haired scalp, more frequently on the bald scalp.
- It can be the consequence of radiation damage or of arsenic exposure.
- Basal cell carcinoma can occur on nevus sebaceous or as part of a genetic syndrome called Gorlin–Goltz syndrome.
- It can also be the consequence of long-standing immunosuppression

About 20% of basal cell carcinomas of the maxillofacial region are localized on the scalp.

Basal cell carcinoma of the scalp is more common in women (Fig. 18.2) than in men. It may also occur in children and is not limited to the bald scalp.

Risk factors for scalp basal cell carcinoma include UV radiation, radiotherapy and immunosuppression [5]. Basal cell carcinoma is a well-known long-term complication of radiotherapy (Fig. 18.3) for tinea capitis, with an estimated risk of 4.9%. In these patients multiple tumors, usually the nodular or cicatricial types, are frequent, even if the scalp does not show signs of radiodermatitis (Fig. 18.4) (Table 18.2) [8, 12].



Fig. 18.2 Basal cell carcinoma of the scalp and frontal hairline in a 75-year-old woman

Table 18.2 Radiation-induced scalp tumors

11.6% of scalp neoplasms
Latency period 36 + / -14 years
Basal cell carcinoma 83%
Squamous cell carcinoma 11%
Chronic radiodermatitis 38%
"Normal looking scalp" 62%

Multiple scalp basal cell carcinomas are also seen in renal transplant recipients or in Gorlin–Goltz syndrome, an autosomal-dominant disorder with a high degree of penetrance and a variable expressivity characterized by several development defects and a predisposition to cancer. Intracranial invasion is an extremely rare complication, as is local lymph node metastasis.

18.5.1 Treatment Options

The classical way of treating basal cell carcinoma is excisional surgery. In sclerodermiform basal cell carcinoma Mohs surgery is performed; in superficial basal cell carcinoma or in elderly patients where surgery is not feasible cryosurgery can be used. Photodynamic therapy and Nd:YAG laser treatment can also be an option.

5-Fluorouracil cream (5%) can be utilized for small superficial basal cell carcinoma, with 90% lesions cured in about 10 weeks of application.



Fig. 18.3 Large, ulcerated basal cell carcinoma in chronic radiodermatitis of the scalp

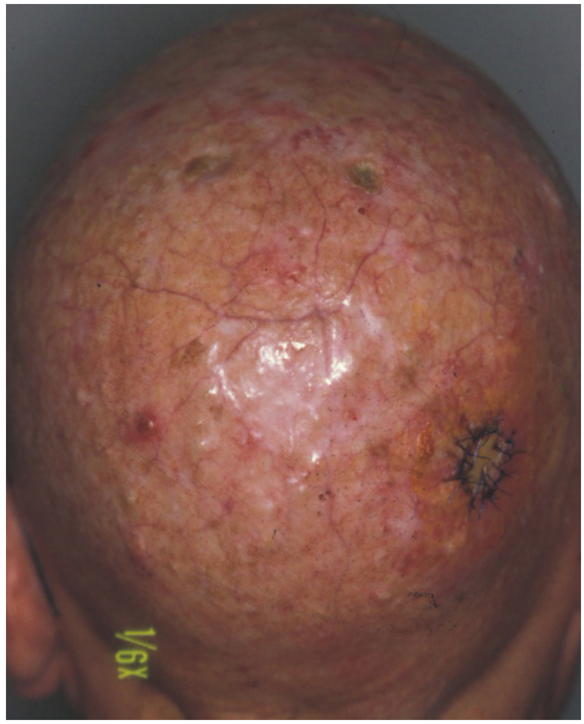


Fig. 18.4 Chronic radiodermatitis of the scalp

18.6 Squamous Cell Carcinoma

Synonyms
spinous cell cancer, cancer of the scalp

Key Features

- Rare tumor, mainly occurring in elderly bald men.
- More frequent in transplant recipients.

Scalp squamous cell carcinoma is quite rare and more frequent in elderly bald males. It usually arises on actinic keratosis. Other risk factors include radiotherapy, chronic lupus erythematosus, and immunosuppression: squamous cell carcinoma is frequent in renal transplant recipients, especially in males [11].

18.6.1 Treatment Options

- Excisional surgery.

18.7 Primary Melanoma of the Scalp

Synonyms
malignant melanoma

Key Features

- Rare, 2%–5% of all skin melanomas.
- Males 60% cases.
- Poor prognosis due to its late discovery and treatment.
- At the same thickness has same prognosis as melanoma of other sites.

Melanoma of the scalp is not as common as melanoma at other body sites but its contribution to melanoma deaths is significant.

In a large study [4] from large series of cases of primary melanoma fewer than 3% were localized on the scalp.

Scalp melanomas often arise within congenital nevi in children and young adults, or within a lentigo maligna in the sun-damaged bald scalp of elderly men. Clinical presentation is similar to that of melanoma on other sites.

Melanoma of the scalp is known as "the invisible killer" of the skin [2]. The melanoma's location has an effect on the prognosis, with lesions that occur posterior to the tragal line (hair-bearing area) having the worst prognosis [19]. Due to its often late discovery and treatment scalp melanoma has a poorer prognosis than melanoma at many other body sites [15]. The prognosis of melanoma of the scalp is the same as that of melanomas with the same Breslow thickness in other sites; however, the average 5-year survival rate of the scalp melanoma is comparatively poor (less than 20%).

18.7.1 Lentigo Maligna

Lentigo maligna is a type of melanoma in situ. Scalp lesions are common on sun-damaged bald areas. Invasive melanoma is said to occur in 5%–10% of cases of lentigo maligna (over a period of 20 years).

18.7.2 Desmoplastic Melanoma

The scalp is the most common site of desmoplastic melanoma. This tumor is a rare type that usually lacks the typical clinical features of melanoma. Desmoplastic melanoma usually appears as a non-pigmented nodule that is difficult to diagnose and can be mistaken for scar tissue or a benign fibrosing tumor.

18.7.3 Treatment Options

Melanoma of the scalp should be treated aggressively. Early detection and subsequent surgical excision with an adequate margin of surrounding uninvolved skin are the key points needed to obtain a favorable prognosis [7].

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18.8 Angiosarcoma

Synonyms

malignant angioendothelioma, hemangioendothelioma, hemangioblastoma

Key Features

- Rare.
- Elderly men.
- Insidious clinical presentation.
- Poor prognosis.

Angiosarcoma is a rare aggressive neoplasm that predominantly affects elderly patients [10].

Clinically, the tumor initially presents as a poorly defined gradually enlarging bruise-like plaque that simulates a hematoma. With time the lesion develops areas of nodularity and may eventually ulcerate. Multifocal lesions are frequent. Hair may be normal, thinned or more rarely lost with extensive cicatricial alopecia.

Metastases occur to lymph nodes and lungs and prognosis is rather poor with a survival rate at 5 years of less than 15%.

18.8.1 Treatment Options

Although the optimal treatment is excisional surgery followed by wide-field radiotherapy, the disease is frequently so extensive at diagnosis that it is not completely resectable.

Chemotherapy with paclitaxel is another option [14].

18.9 Scalp Metastases

Key Features

- Most commonly misdiagnosed as epidermoid cysts.
- Most commonly originate from breast and lung cancer.
- Rare, but possibly the initial presentation of an internal malignancy.
- Nodular lesions.
- Treat the primary tumor.

Cutaneous metastases occur in 2%–4% of patients with internal carcinoma, and the scalp is a relatively frequent site (12% of all skin metastases) because of its abundant blood supply. Sometime a metastasis may be the initial presentation of an internal malignancy.

Scalp metastases frequently present as either single or multiple firm non-tender bald nodules. A solitary nodule is the most frequent presentation.

Due to their appearance, they are common misdiagnosed as epidermoid cysts.

In males, the primary tumor is usually localized in the lung, colon, stomach, or kidney.

In women, breast and lung cancers are the commonest causes of cutaneous metastases.

Rarely a scalp metastasis originates from pancreas, liver, uterus or bone malignancies.

Meningiomas may also involve the scalp either through direct extension, through an operative defect, or by metastasis.

18.9.1 Scalp Metastases from Lung Cancer

The incidence of cutaneous metastases from lung cancer varies from 2.8% to 7.5%. The scalp represents 4% of all cutaneous metastases. Most patients with scalp metastases of lung cancer die within a few months. The average interval between the appearance of skin lesions and death in three patients with squamous cell carcinoma of the lung was 0.8 months [20].

18.9.2 Scalp Metastases from Breast Cancer

In women, the scalp is a site of metastasis particularly of carcinoma of the breast. Breast cancer metastases may appear even years after the primary tumor was surgically removed.

18.9.3 Scalp Metastases from Colon Cancer

Colorectal carcinoma is the second most common carcinoma to metastasize to the skin after carcinoma of the lung. Skin metastases from bowel carcinoma usually indicate advanced disease and a poor prognosis [1].

18.9.4 Scalp Metastases from Gastric Cancer

Metastatic dissemination of gastric carcinoma to the skin usually occurs in advanced stage disease. Scalp metastases are uncommon and exceptionally are the first sign of disease.

18.9.5 Scalp Metastases from Renal Cancer

Renal cell carcinoma may metastasize to the skin of the scalp. This rare presentation is often associated with a poor prognosis.

18.9.6 Scalp Metastases from Esophageal Carcinoma

There are few reported cases of scalp/cutaneous metastases of esophageal carcinoma, but reports may become more common as the incidence of esophageal cancer increases.

18.9.7 Treatment Options

Early detection and subsequent biopsy should be made. Treatment of the primary lesion is mandatory; metastases can be excised but also be kept as a marker lesion during chemotherapy.

18.10 Metastatic Carcinoma of the Scalp

Synonyms
alopecia neoplastica

Key Features

- Single/multiple alopecic patches.
- Most common cause is breast carcinoma.
- Can resemble alopecia areata or scarring alopecia.

Alopecia neoplastica is a rare form of alopecia in which the hair follicle is directly involved in the neoplastic process. The most common cause is metastatic breast carcinoma; it may resemble localized alopecia areata or scarring alopecia [3, 18].

Alopecia neoplastica without alopecia has been described; in this case metastatic spread to the scalp produced clinically inconspicuous alopecia [9].

18.10.1 Treatment Options

If is not possible treat the primary lesion the prognosis is poor.

18.11 Lymphomas

18.11.1 Non-Hodgkin's Lymphomas

Non-Hodgkin's lymphomas can involve the scalp. Primary cutaneous lymphomas are the second most common site of extranodal non-Hodgkin's lymphoma.

18.11.2 Mycosis Fungoides, Follicular Mycosis Fungoides and Sézary Syndrome

Key Features

- Follicular lesions with or without mucinosis.
- Poor prognosis due to deep location of the neoplastic infiltrate.
- Face and scalp lesions (Fig. 18.5).
- Comedo-like and cystic lesions.
- Lymphocytic infiltration with pilotropism.
- Lymphocytic atypia with clonal rearrangement of the lymphocytic infiltrate.



Fig. 18.5 Alopecia, scalp nodules and ulcerations in mycosis fungoides

Alopecia in mycosis fungoides is usually, but not exclusively, caused by follicular mucinosis. Alopecia can be misdiagnosed as alopecia areata and may involve the scalp or other body areas.

Follicular mycosis fungoides is an uncommon variant of mycosis fungoides that causes patchy alopecia, resembling alopecia areata, comedo-like lesions and cysts (Fig. 18.6). The prognosis is poor [21].

Sézary syndrome frequently causes diffuse alopecia.

18.11.3 Follicular Mucinosis

Follicular mucinosis can be associated with mycosis fungoides or Sézary syndrome or be an isolated finding, i.e., idiopathic follicular mucinosis. Idiopathic follicular mucinosis usually affects young individuals and is considered a non-aggressive localized variant of mycosis fungoides with excellent prognosis.

In mycosis fungoides, follicular mucinosis produces erythematous indurate bald patches on scalp, beard, and eyebrows (Fig. 18.7). The follicular orifices are often prominent.

Idiopathic follicular mucinosis produces single or multiple patches of alopecia on the scalp, trunk, and limbs. The pathology shows a lymphoid infiltrate around and within hair follicles and deposits of mucin within the hair follicle.

Differentiation between idiopathic mucinosis and mycosis-fungoides-associated follicular mucinosis is often impossible, even with polymerase chain reaction (PCR) analysis of the infiltrate, since a monoclonal T-lymphocyte population is found in both types.

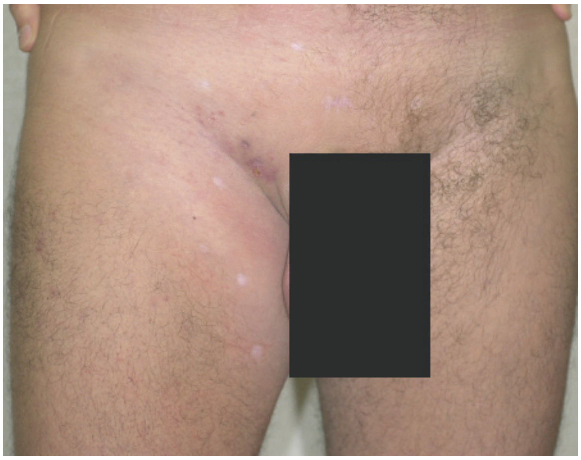


Fig. 18.6 Follicular mycosis fungoides producing alopecia of the groin in a young man

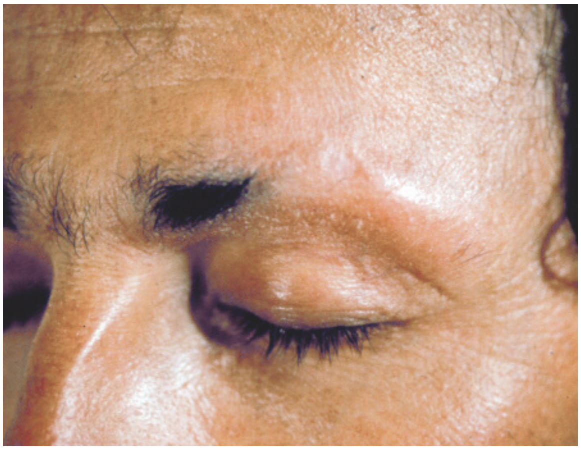


Fig. 18.7 Follicular mucinosis due to mycosis fungoides of the eyebrow: indurated alopecia

18.12 Scalp Hemangiomas

Key Features

- Common benign congenital vascular neoplasms.
- Location: 60% of hemangiomas are located on the head and neck.
- More common in premature infants and white females.
- Development within the first weeks or months of life.
- Gradual regression after 12–18 months of age with minimal or no residua.

Capillary hemangiomas are benign vascular lesions that commonly present at birth or in early infancy. In most cases hemangiomas appear within the first few weeks of life and grow rapidly during the first year.

Clinically, hemangiomas first appear as a pale, blanched area of the skin that with time reddens and progressively enlarges.

Without treatment, most infantile hemangiomas spontaneously involute over a course of years, and 90% reach maximal regression by 9 years of age.

Intracranial hemangiomas are uncommon, especially in the absence of diffuse hemangiomatosis or the PHACES syndrome (posterior fossa malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, eye abnormalities, sternal clefting, and/or supra-umbilical raphe).

18.13 Epidermoid Cyst

The epidermoid cyst is an ordinary benign tumor that frequently develops on the scalp. The lesions appear as a mobile, elastic, and soft nodule adherent to the scalp surface. The lesion may become inflamed and undergo suppuration.

Summary for the Clinician

Scalp tumors are usually benign. In children and young adults, suspect a sebaceous nevus. Actinic keratoses are common in elderly men and usually occur in association with baldness and photodamage. Malignant tumors involving the hairy scalp are often overlooked, as in the case of scalp melanoma that is usually diagnosed with considerable delay as compared with melanoma on other sites. Keep in mind that metastatic tumors of the scalp are not rare and may produce an alopecic area. Close follow-up or biopsies are required in doubtful cases.

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Chapter 19

Disorders of the Scalp

Rodney Sinclair, Yee Jen Tai

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19.1 Tinea Capitis

Synonyms
scalp ringworm

Key Features

- Tinea capitis is caused by dermatophyte infection (*Microsporum* and *Trichophyton* sp.).
- Clinical findings include well-demarcated circular plaques with broken-off hairs.
- Certain *Microsporum* species fluoresce when the scalp is examined with a Wood's lamp.
- Hair and skin scrapings should be sent for culture if there is a clinical suspicion.
- Treatment is with oral antifungal agents such as griseofulvin.

19.1.1 Introduction

Tinea capitis is the invasion of a scalp hair by dermatophyte fungi. With the exception of *epidermophyton*, nearly all dermatophytes are able to parasitize hair.

19.1.2 History

Raymond Sabourand, a French dermatologist, played an important role in establishing the status and characteristics of the dermatophyte species. Further taxonomic studies have since clarified the classification of these organisms.

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19.1.3 Epidemiology

The organisms causing tinea capitis vary from country to country. Pathogenic organisms are classified into the genera *Microsporum* and *Trichophyton*. *Microsporum canis* is the dominant organism in Australia [36], although there is increasing incidence of infection with *Trichophyton tonsurans* [47]. The former organism tends to affect only prepubertal children with spontaneous resolution in adolescence. *Trichophyton tonsurans* is the commonest cause among Australian Aborigines and African-Americans.

19.1.4 Pathogenesis

Anthropophilic infections are acquired from person to person contact as well as materials left on hairbrushes, combs, and hats. Trauma assists inoculation. Zoophilic infections are acquired exclusively from animals with the exception of *M. canis*, which can be secondarily spread from person to person in a limited fashion. Geophilic fungal infections are acquired from the soil.

19.1.5 Clinical Features

Microsporum canis infections classically produce circular lesions (Fig. 19.1). Central healing that is normally a feature of tinea corporis is less prominent on the scalp. Fracture of hairs close to the scalp surface give the appearance of alopecia, however the affected scalp is not bald [26]. The broken hairs have a dull gray appearance due to the coating of the arthrospores. There is a characteristic fine scaling to the scalp but inflammation is minimal. The lesions are sharply demarcated. There may be several such patches arranged randomly throughout the scalp. Each patch fluoresces when examined in a darkened room with a Wood's lamp. Scalp lotions and creams should be washed off as these may mask the fluorescence.

The clinical presentation of *Trichophyton tonsurans* is variable. Infection can cause severe damage to affected hairs, inducing them to break off at the scalp surface [6, 49]. This gives rise to black dot ringworm, where the black dots represent broken hairs within an angular patch of alopecia. In other cases there is only mild scaling or inflammation if the scalp and hair loss is minimal. Such cases may be mistaken for seborrheic dermatitis or



Fig 19.1 Tinea capitis (scalp ringworm)

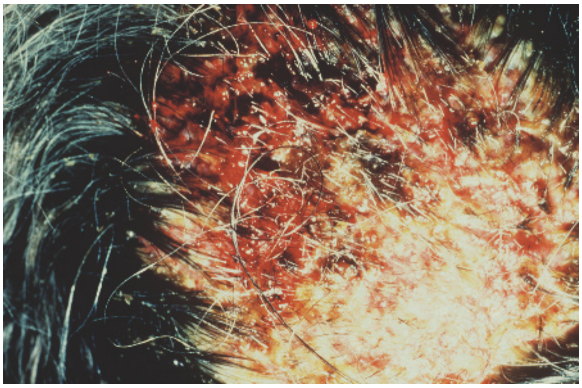


Fig. 19.2 Kerion

Table 19.1 Treatment of tinea capitis

Treatment	Level of evidence
Oral griseofulvin	1
Oral itraconazole	1
Oral terbinafine	1
Oral fluconazole	2

folliculitis if pustules are present. Fluorescence is negative. Diagnosis can be confirmed in suspected cases by microscopy and fungal culture.

Infection with zoophilic or geophilic fungi tends to be more inflamed and a kerion may develop. A kerion is a painful, purulent, inflamed boggy mass (Fig. 19.2). Hairs fall out rather than break off and any remaining hairs can be easily and painlessly pulled out. Thick crusting, with matting of adjacent hairs is common. The usual organisms responsible are *T. verrucosum and T mentagrophytes.* Kerion may heal with scarring and permanent hair loss.

Favus is caused by *T. schoenleinii.* Cutaneous atrophy, scar formation, and permanent hair loss with yellow cup-shaped crusts known as scutula are characteristic features.

19.1.6 Pathology

Hair and skin scrapings should be sent for culture to confirm the diagnosis and to identify the species involved. While the management is not influenced by the species, determination allows an animal or human reservoir to be traced and tested.

Histology of a kerion shows an intense purulent folliculitis. Hyphae can be readily seen on periodic acid Schiff (PAS) staining.

19.1.7 Differential Diagnosis

Seborrheic dermatitis and atopic dermatitis of the scalp can mimic tinea capitis. These conditions tend to be diffuse and less well-demarcated. Hair loss and broken-off hairs are not a feature of psoriasis. Alopecia areata, especially with spontaneous regrowth, can mimic tinea capitis, although erythema and scaling are not features of alopecia areata. Discoid lupus results in erythema, perifollicular hyperkeratosis and permanent hair loss, and may resemble the appearance of the scalp post-kerion.

19.1.8 Treatment

Despite the development of triazole antifungal agents, based on cost and efficacy, the treatment of choice for tinea capitis is still griseofulvin. The optimal dose is 15 mg/kg per day (or 10 mg/kg per day of ultramicrosize griseofulvin) for adults and 10 mg/kg per day for children, and treatment should be continued for continued for 2 weeks beyond clinical and mycological cure [8, 17, 30]. Cultures should be repeated at 4 weeks and every 2 weeks thereafter until mycological cure. Black dot ringworm usually requires longer treatment than *Microsporum* infections.

Alternatives to griseofulvin are terbinafine [8, 17], itraconazole [23], and fluconazole [20] (Table 19.1). Cure rates are similar and shorter treatments are required, however these agents are more expensive.

Children with infection due to anthropophilic fungi and *M. canis* should be kept home from school at least until oral therapy has been initiated. In school epidemics, classmates should be examined with a Wood's light. Topical antifungal shampoos should theoretically reduce contagion, however this has not been rigorously investigated.

19.2 Pediculosis Capitis

Synonyms
nits, head lice

Key Features

- The pathogenic organism in head lice is *Pediculosis humanus capitis*.
- Pediculosis presents as pruritus predominantly in the occipital region of the scalp, with occasional papules.
- Diagnosis is by identification of the arthropod or its eggs, which can be aided by examination with either a Wood's lamp or a dermatoscope.
- Many cases of scalp pediculosis are now resistant to organochloride insecticides and permethrin. Regular scalp combing after pre-treatment with conditioner is the principle treatment for multi-resistant lice.

19.2.1 Introduction

Pediculosis humanis is divided into *Pediculosis humanus capitis* (head louse) and *Pediculosis humanis corporis* (body louse). The *Pediculosis humanis capitis* louse feeds on the skin of the scalp and deposits her eggs (nits) on the hair. It is occasionally found on the body, but *Pediculosis humanis corporis* tends not to wander onto the scalp.

19.2.2 History

Primates and their lice have been co-speciating for over 20 million years. Modern humans have two genetically distinct types of lice that segregated 1.18 million years ago. Old World head lice, but not New World head lice have the ability to transform into body lice within a few generations but reverse transformation (body into head louse) is not known [46].

The Old World head louse is found worldwide and evolved on the ancestors of our species, *Homo sapiens*. The New World head louse is found only in the Americas and evolved on *Homo erectus*, another early human species, but jumped to *Homo sapiens* about 25,000 years ago [46].

This host switch is considered to be primae facie evidence of direct physical contact between modern and archaic forms of *Homo* [46].

As body lice live in clothing and only have contact with the skin to feed once or twice a day, their success depends on their hosts being clothed. Body lice are vectors for the bacteria responsible for epidemic typhus, trench fever, and relapsing fever; head lice are not known to vector any agent of human disease under natural conditions.

19.2.3 Epidemiology

Head lice infestations generally occur in epidemics, particularly among school children. This may be a result of the behavior patterns that children at different ages exhibit [13]. It is also more prevalent in poverty-stricken overcrowded areas.

19.2.4 Pathogenesis

The female head louse is 3–4 mm long. The male is slightly smaller and banded across the back. During her 40-day life span, the female lays approximately 300 eggs at a rate of 8 eggs/day. The eggs are oval, white capsules with a lid (operculum) and are firmly cemented to the side of the hair shaft adjacent to the scalp (Figs. 19.3, 19.4). After about a week the larvae hatch close to the scalp. Larvae resemble small adults and begin feeding on the blood of the host soon after hatching. After undergoing three moults in 10 days, the louse reaches maturity and commences mating. In most established infestations of head lice there are fewer than 10 adult lice. Counts of more than 100 are uncommon. Most infections are acquired by direct head-to-head contact but combs, brushes, and hats are also responsible for some infections.



Fig. 19.3 Pthirus pubis. The crab louse



Fig. 19.4 Juvenile head louse (nit) attached to hair shaft

19.2.5 Clinical Features

Pruritus is variable. It is often intense and only rarely absent [39]. It is usually worst in the occipital region where the infestation is the heaviest. Papular lesions can occasionally be seen in the nape of the neck and may become generalized [48]. Scratching can lead to impetiginization and the hair may become matted down by exudate to produce "plica polonica." Nits can be seen with the naked eye and are very easily seen with a Wood's light or with a hand-held epiluminescent microscope (dermatoscope). This is useful for screening in schools during epidemics. Pediculosis is rare in black people as the lice appear not to grab tightly curled hair as well [11].

19.2.6 Pathology

The diagnosis of infestation should only be accepted when the insect or its eggs have been positively identified. Peripilar hair casts or pseudonits are a source of confusion [54], but these can be readily slid up and down the hair shaft and are circumferential rather than eccentric. This can be visualized by light microscopy.

19.2.7 Differential Diagnosis

Pediculosis capitis should be distinguished from other diseases of the scalp that can cause pruritus such as seborrheic dermatitis, atopic dermatitis, and psoriasis.

19.2.8 Treatment

In the presence of severe pruritus, scratching may cause secondary bacterial infection, for which systemic antibiotics are usually required.

In most countries a number of insecticides are available for the treatment of head lice. Most are available over the counter and do not require prescription from a medical practitioner. Commonly used agents include lindane, malathion, carbaryl, natural pyrethroids and the synthetic pyrethroid permethrin.

There are growing numbers of treatment failures due to the emergence of treatment-resistant lice [12]. In many countries the lice are resistant to all insecticides. Regular scalp combing after pre-treatment with conditioner is the best way to screen for lice infestation and the best way to confirm eradication of lice following insecticide treatment. It is also the principle stand-alone treatment for multi-resistant lice. For girls with very long hair, this treatment is easier to apply and more successful after the hair has been cut to shoulder length. Similarly boys also benefit from cutting the hair when long.

Initial treatment should be with an insecticide selected on the basis of known local resistance behavior of the lice (Table 19.2).

Malathion and carbaryl are acetylcholinesterase-inhibiting insecticides [35, 37, 38]. They should be left in the scalp for 12 hours before being washed off. Blow-drying should be avoided as heat degrades these insecticides. Both agents effectively kill lice, however they do not kill all the eggs and a second application after 7–10 days is usually recommended. Malathion coats the hair, making it resistant to re-infection with susceptible strains for up to 6 weeks.

Lindane is an organochloride antiseptic. Due to potential toxicity to infants its availability is restricted in many countries.

Permethrins [57] generally require a 10-min scalp application after shampooing. This is repeated after 7–10 days. Again hair dryers should be avoided.

None of these treatments removes dead nits. Combing with a fine-toothed comb is tedious and painful. Nits will eventually wear away after repeated washing. A cream rinse containing 8% formic acid can be used as a nit-remover.

Table 19.2 Treatment of *Pediculosis capitis*

Treatment	Level of evidence
Topical permethrin	1
Topical carbaryl	2
Topical malathion	2
Topical lindane	2
Topical ivermectin	2

Most schools have a policy on head lice infestation. The most rational policy is for infected children to be kept home from school until the first treatment is completed.

19.3 Seborrheic Dermatitis

Synonyms
dandruff, pityriasis capitis

Key Features

- Seborrheic dermatitis affects areas that are dense with sebaceous glands.
- It has a predilection for patients with acquired immunodeficiency syndrome (AIDS) and patients with neurological conditions.
- The pathogenic factors in this condition include sebum production, *Malassezia* sp. colonization and the immune system.
- Clinical features can range from fine scaling of the scalp to erythematous patches with waxy scale crusted with exudate.
- Most cases can be treated with anti-dandruff shampoos containing selenium sulfide, zinc pyrithione, tar or antifungal agents.

19.3.1 Introduction

Seborrheic dermatitis is an inflammatory condition of the skin most commonly occurring on the scalp, face, and chest. The term dandruff or pityriasis capitis corresponds to a milder form of seborrheic dermatitis resulting in fine scaling of the scalp.

19.3.2 History

Willan first described pityriasis as irregular patches of small thin scales. Hebra later elaborated this further in 1870 by introducing the term seborrheic oleosa to emphasize the role of sebaceous glands in its pathogenesis [9].

19.3.3 Epidemiology

Seborrheic dermatitis affects 1%–3% of immunocompetent adults [19]. It is more common in adolescents and young adults, with the incidence increasing again after the age of 50 years. This condition can also occur in infants, commonly termed “cradle cap” when it occurs on the scalp. The condition is often self-limiting, starting at around 6 months and subsiding at about 8 months of age. It has a seasonal variation, often becoming more severe in the winter months. This condition also has a predilection for patient with AIDS and patients with neurological conditions such as Parkinson’s disease, epilepsy, and spinal cord injury. The incidence in AIDS patients can be between 34% [5] and 83% [32] and is directly related to T cell count.

19.3.4 Pathogenesis

The cause of seborrheic dermatitis is unknown. It is thought to result from a combination of factors. One factor is the sebum level, which accounts for the fact that this condition occurs more commonly in adolescents when sebaceous glands are most active. The distribution of the lesions also supports this, being more common on the scalp, face, chest, and back. *Malassezia* yeasts have also been implicated in this condition. While previously *Malassezia furfur* was thought to be the pathogenic yeast, more recent studies have identified *Malassezia globosa* and *Malassezia restricta* as the pathogens [20, 21, 40]. It is thought that the pathogenesis of this condition is also related to the immune response. Various studies have shown that seborrheic dermatitis may be related to depressed T cell function, increased prevalence of natural killer cells, elevated total IgG antibodies, activation of complement, and an increase in inflammatory interleukins [4, 14].

19.3.5 Clinical Features

Pityriasis capitis by itself is not pruritic. Any association with seborrhea of the scalp appears to be coincidental, as marked scaling can occur in the absence of seborrhea and vice versa. Examination of the scalp would reveal widespread small, thin, white or grayish loose scales that fall from the scalp onto the shoulders.

In seborrheic dermatitis, there are large waxy yellow scales combined with exudate that forms a crust beneath which the scalp is erythematous and moist (Fig. 19.5). Perifollicular erythema and scaling may extend to form well-demarcated erythematous plaques. Excoriation may result in secondary impetiginization,



Fig. 19.5 Infantile seborrheic dermatitis

occasionally with pustulation. Other features of seborrheic dermatitis may be present such as retroauricular scaling, blepharitis, and a facial rash that centers on the nasolabial folds.

19.3.6 Pathology

The scales of pityriasis capitis and seborrheic dermatitis correspond to parakeratosis, which overlies areas of hyperproliferative epidermis. Spongiosis, epidermal acanthosis, dermal edema, and superficial perivascular lymphohistiocytic infiltrate are features of early seborrheic dermatitis. Longer-standing lesions develop follicular plugs of orthokeratotic and parakeratotic cells with uneven rete ridges.

19.3.7 Differential Diagnosis

Psoriasis may resemble seborrheic dermatitis, but the scale in psoriasis is often heavier with a silvery appearance. Lichen simplex chronicus over the occiput may also cause confusion; however, the characteristic site, the intensity of the itching, and the persistence of the plaque as a solitary lesion strongly suggest that diagnosis. Tinea capitis, especially due to *Trichophyton tonsurans*, may closely mimic seborrheic dermatitis. Examination with Wood's lamp and fungal scrapings should be done if there is any clinical suspicion of dermatophytosis.

19.3.8 Treatment

Pityriasis capitis can be effectively treated with a large number of agents available over the counter (Table 19.3). It is important for the patient to be aware that this is a relapsing condition that may require maintenance treatment. The aim of treatment is to suppress the scaling at the lowest possible cost and inconvenience. Antidandruff shampoos are readily available and effective in most cases. Common active ingredients include selenium sulfide [10], zinc pyrithione [33], ketoconazole, miconazole, and ciclopirox [29]. Tar-based shampoos are also effective in many cases, but have low patient acceptability due to the fragrance [44].

Treatment success depends not only on the active ingredient, but also on particle size and shape, which in turn affects dispersion of the active ingredient on the scalp, and adherence to the scalp. Insufficient coverage of the scalp occurs when particles are too large. In contrast particles that are too small adhere poorly. Optimal particle size is 2.5 µm. Formulation of zinc pyrithione in platelet particles enables the shampoo to be rinsed off immediately without loss of efficacy. This improves patient compliance and the likelihood of treatment success. Antidandruff shampoos can now be compounded together with conditioning agents, which also improves the esthetics of the shampoo and patient compliance.

Failures most commonly result from insufficient usage, either because the hair is not washed frequently enough or the instructions regarding how long to leave the shampoo on the scalp prior to rinsing are not followed. Shampoos without conditioning agents have low patient acceptability and switching to non-medicated shampoos commonly results in relapse.

Topical corticosteroids are generally reserved for severe or refractory cases, although long-term use can be associated with adverse effects such as atrophy, telangiectasia, and altered scalp sensation.

Oral therapy can be used in severe cases of seborrheic dermatitis that do not respond to conventional topical therapy. This includes ketoconazole [16], itraconazole [27], and terbinafine [50].

Table 19.3 Treatment of seborrheic dermatitis

Treatment	Level of evidence
Ketoconazole shampoo	1
Ciclopirox shampoo	1
Selenium sulfide shampoo	1
Zinc pyrithione shampoo	2
Topical miconazole	3

19.4 Psoriasis

Key Features

- Scalp is commonly affected in psoriasis, and can occur in isolation.
- Lesions are sharply demarcated erythematous plaques with thick silvery scale.
- Histological features include psoriasiform acanthosis with elongation of rete ridges and suprapapillary thinning.
- Treatment often requires a combination of tar, salicylic acid and dithranol.

19.4.1 Introduction

Psoriasis is a polygenic familial, chronic papulosquamous inflammatory dermatosis that commonly affects the scalp. It is associated with HLA-CW6 [18].

19.4.2 History

For many centuries psoriasis was confused with leprosy. In the late eighteenth century Robert Willan, an English dermatologist, differentiated it from other skin diseases and provided the first rational nomenclature based on the appearance of lesions. In 1841 the condition was named *psoriasis* by the Viennese dermatologist Ferdinand von Hebra. The name is derived from the Greek word *psora* which means to *itch*.

19.4.3 Epidemiology

Psoriasis affects between 2% and 5% of the population [45]. Scalp involvement is a prominent feature and often the initial presentation. This condition may appear at any age, but age of onset has bimodal peaks in the teens and again in the sixties [15].

19.4.4 Pathogenesis

The pathophysiology involves abnormal hyperproliferation of the skin with a rapid cell turnover time in the epidermis (3–4 days). This is now considered to be secondary to activation of the cellular immune system producing a variety of cytokines (especially tumor necrosis factor alpha, TNF α), eicosanoids (especially leukotriene B4) and polyamines. The cytokine profile in psoriasis is consistent with a type-1 T helper cell (Th1) response. The changes in epidermal kinetics result in alterations in the epidermal cell keratin cytofilament expression and cellular differentiation [3].

19.4.5 Clinical Features

Lesions of psoriasis consist of well-demarcated erythematous plaques with a classical silvery scale that bleeds when scratched off (Auspitz sign). Pruritus is variable, with many sufferers relatively untroubled and some extremely distressed by it.

Scalp involvement occurs in about 79% of psoriatics and may be the first and occasionally the only manifestation of psoriasis [59]. Initially, they may only be

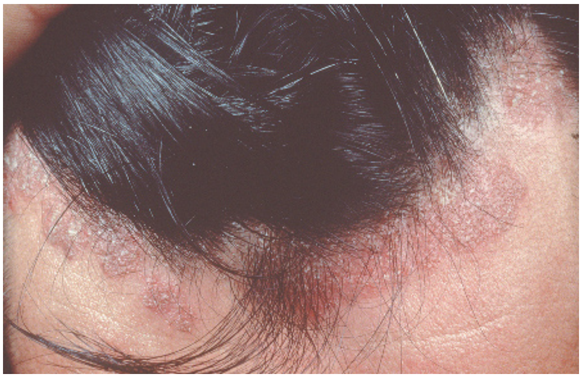


Fig. 19.6 Psoriasis along the anterior hair line

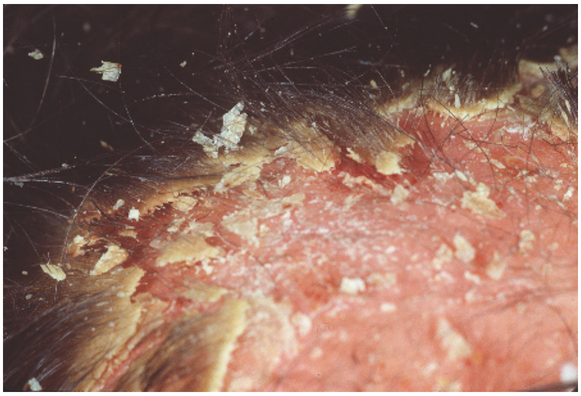


Fig. 19.7 Psoriasis erythematons plague with thick scaling and hair loss

patch or diffuse scaling without any specific features. A thick scale crust that encases and binds down hairs (pityriasis amiantacea) may develop. More commonly, palpable plaques covered with thick scale develop that may extend just beyond the hairline (Figs. 19.6, 19.7). Any part of the scalp can be involved and there may be some mild thinning of the hair overlying the plaques, although uncommon. Trichograms of plucked hair from psoriatic scalp have indicated a telogen effluvium [51]. Scarring alopecia associated with psoriasis has also been described [53]. The scalp lesions frequently irritate or itch, but severe pruritus is very rare. A seronegative arthritis can occur in 20% of patients with psoriasis.

19.4.6 Pathology

Psoriasis is a dynamic process and the histology of a lesion varies during its evolution and subsequent regression. Well-developed lesions show psoriasiform acanthosis with suprapapillary thinning of the epidermis and edematous dermal papillae. The granular layer of the epidermis is thinned and there is parakeratosis. Occasionally Munro's microabscesses occur, which are collections of neutrophils in the stratum corneum. There is follicular plugging, enlargement of the follicular ostia, and follicular parakeratosis. The epidermis may show spongiosis with collections of neutrophils forming spongiotic pustules. In the dermis, there is a superficial perivascular mixed cellular infiltrate. Despite the increased epidermal proliferation and reduced transit time, the rate of hair growth is not increased. However, the caliber of hairs from within a plaque is reduced and the cuticles are ruffled.

19.4.7 Differential Diagnosis

Seborrheic dermatitis may be diagnostically confused with psoriasis especially in the absence of skin lesions elsewhere or nails changes. Retroauricular involvement suggests seborrheic dermatitis as do fine powdery scales, whilst thick large silvery scales suggest psoriasis. Occasionally, it is impossible to differentiate between the two conditions until lesions appear elsewhere on the body. Atopic dermatitis of the scalp with secondary lichen simplex chronicus may look similar morphologically to psoriasis but severe pruritus is often a distinguishing feature of the former. Pityriasis rubra pilaris bears much similarity to psoriasis clinically and histologically.

19.4.8 Treatment

Tar shampoos containing 2%–10% coal tar solution should be the first-line approach for mild cases of scalp psoriasis [42]. Steroid scalp lotions are useful for pruritus [25], but thick scale can act as a barrier for these lotions. These may need to be removed prior to application of steroid lotions. The lotion is applied to the scalp after hair has been parted and left overnight.

Thicker plaques or resistant cases will require a tar pomade left on overnight [24]. Coconut oil-based or cade oil-based tar and salicylic acid pomades [28] may be very useful. Other options include dithranol pomades [55], but this has to be used cautiously in fair-haired psoriatics as it may stain blonde hair mauve, and should be rinsed out sooner in psoriatics with blonde hair as it may cause irritation.

Prior application of salicylic acid (10%–25%) in mineral oil to the scalp for 30 min to loosen the scale and then combing the hair with a fine-tooth comb to remove the scale will enhance the action of the pomades.

To apply the pomade, the hair is parted with a comb and the ointment applied down the part. The hair is the re-parted a little further along and the tar reapplied. The part is moved again until the entire scalp has been treated. A shower cap or a Tubifast bandage is applied over the top to protect the pillowcase. Plastic shower caps should never be used in children who are at risk of suffocation beneath them. The treatment is then washed off in the morning with a tar shampoo. Pomades are messy and patients need to be motivated.

Systemic treatments (Table 19.4) also help with scalp psoriasis but are rarely indicated for scalp psoriasis in isolation. UV B and psoralen UV A therapy (PUVA) are of little benefit as the scalp is shielded from the light by the hair. Any systemic effect of PUVA tends to be small and unpredictable.

Table 19.4 Treatment of psoriasis

Treatment	Level of evidence
Coal tar	1
Topical corticosteroids	1
Dithranol	2
Salicylic acid	3

19.5 Atopic Dermatitis of the Scalp and Lichen Simplex Chronicus

Synonyms
eczema of the scalp

Key Features

- It is unusual for atopic dermatitis to occur in isolation on the scalp.
- Chronic excoriation of the scalp results in lichen simplex chronicus.
- Secondary infection with *Staphylococcus aureus* is a common complication.
- Spongiosis is a histological hallmark of atopic dermatitis.
- Treatment involves tar shampoos, topical, and oral corticosteroids.

19.5.1 Introduction

Atopic dermatitis is a chronic pruritic inflammatory dermatosis that can occasionally affect the scalp. Chronic pruritus and excoriation can lead to development of lichen simplex chronicus.

19.5.2 History

Atopic dermatitis is now the preferred name for atopic eczema.

19

19.5.3 Epidemiology

Atopic dermatitis affects up to 10%–15% of the population and about 30% of the population are atopic [34, 52]. In 50% of cases, it first presents in infancy but may first appear in any age.

19.5.4 Pathogenesis

Most patients with atopic dermatitis have a heterozygous loss of function mutation of the fillagrin gene [43]. Patients with atopic dermatitis have only one functional copy of this gene that is involved in skin barrier function. One copy of the gene is sufficient for normal skin barrier function under normal circumstances, however when the skin is irritated, the skin barrier is disrupted allowing increased transepidermal water loss and also entry of foreign antigens and infectious agents into the epidermis, where they initiate an immune response.

The immune response tends to be an IgE-mediated late phase response and cell-mediated immunity involving type-2 T helper cells (Th2). Among the pathogenic cytokines secreted by Th2 cells are interleukins-4, -5, -10, and -13, interferon gamma and tumor necrosis factor beta [41]. Th2 cells also stimulate a B cell immunoglobulin production switch to IgE, which has been found on epidermal dendritic cells in atopic individuals [7].

19.5.5 Clinical Features

Involvement of the scalp is often associated with atopic dermatitis elsewhere in the body (Fig. 19.8). It can coexist with simple flexural atopic dermatitis but, more



Fig. 19.8 Severe atopic dermatitis with secondary impetigo

commonly, is related to erythrodermic atopic dermatitis. Clinically, it presents as an itchy, scaly dermatitis of the scalp. Broken hairs can be seen from scratching and rubbing.

With repeated excoriation, the scalp can become lichenified, where the skin is thickened and leathery in texture. Any itchy rash can cause the patient to scratch to gain temporary relief. If the itch returns more severely after a brief intermission and produces renewed scratching, then the patient can fall victim to a repetitive itch-scratch cycle that ultimately produces lichenification. When the original rash is obvious the lichenification is considered secondary, while if the original rash is obscure, the condition is considered lichen simplex chronicus.

Secondary infection is a common complication, frequently with *Staphylococcus aureus*. Herpetic infection can potentially complicate atopic dermatitis, with a resultant Kaposi's varicelliform eruption, however the scalp is often spared.

Childhood atopic dermatitis with prominent scalp involvement can be a feature of a number of inherited syndrome, such as Wiskott-Aldrich syndrome (atopic dermatitis, thrombocytopenia, impaired immunity with elevated IgE, and early death from infection), hyperimmunoglobulin E syndrome (atopic dermatitis, recurrent infections, growth failure and raised serum IgE) and hypereosinophilic syndrome (atopic dermatitis, hypereosinophilia, and multisystem involvement).

19.5.6 Pathology

Spongiosis is the histological hallmark of atopic dermatitis. All other features are variable and non-diagnostic.

19.5.7 Differential Diagnosis

Although this condition can be mimicked by other inflammatory dermatoses of the scalp such as seborrheic dermatitis and psoriasis, the marked pruritus and presence of atopic dermatitis elsewhere in the body are often reliable distinguishing features. Tinea capitis needs to be excluded by examination with Wood's lamp and fungal scrapings if there is clinical suspicion of this.

19.5.8 Treatment

Tar shampoos and pomades [61] as well as steroid lotions and creams can be used [60] (Table 19.5). Oral antibiotics are used for secondary bacterial infection, and oral prednisolone may be required in severe cases [55].

Table 19.5 Treatment of atopic dermatitis of the scalp and lichen simplex chronicus

Treatment	Level of evidence
Topical corticosteroids	1
Coal tar	4
Systemic corticosteroids	5

19.6 Contact Dermatitis

Synonyms
contact eczema

Key Features

- This condition can be divided into irritant contact dermatitis and allergic contact dermatitis, which is more common.
- Contact dermatitis is secondary to agents such as hair dyes, bleaching preparations, thioglycolates, permanent wave solutions, and hair creams.
- Patch testing should be done if there is a suspicion of an allergic contact dermatitis.
- Treatment involves topical corticosteroids and avoidance of the causal agent.

19.6.1 Introduction

Contact dermatitis is an eczematous dermatitis caused by an external agent.

19.6.2 History

The earliest description of contact dermatitis was as early as 2000 bc. At the time, irritant contact dermatitis occurred when extract of the castor oil bean was applied to the scalp for hair growth.

19.6.3 Epidemiology

The prevalence of contact dermatitis varies from 2% to 6% from studies of populations with hand dermatitis [1, 56]. The scalp is usually relatively spared.

19.6.4 Pathogenesis

Contact dermatitis may result from an irritant agent or an allergen. Irritants are abrasive substances with the potential to produce a dermatitis in any individual, while allergens produce a dermatitis in people who are sensitized to that substance and who mount an immunological reaction to it whenever it is encountered.

The scalp is generally resistant to irritants because of its rapid epidermal turnover and the thick stratum corneum layer. Perhaps this is the reason why atopic dermatitis often spares the scalp. The commonest causes of irritation are overuse of bleaching preparations, frequent blow drying, and thioglycolates used in permanent waving (to disrupt disulfide bonds within the hair keratins and allow remodeling of the hair).

Allergic contact dermatitis is more common then irritant dermatitis although the scalp is also relatively resistant to allergens. The initial sensitization may occur on the scalp or at distant sites. The major allergens are permanent (e.g., paraphenylenediamine) and semi-permanent hair dyes (Fig. 19.9), bleaches, permanent wave solutions, and hair creams.

19.6.5 Clinical Features

The scalp margins tend to be worst affected. Allergy can also occur to hair nets, hat bands or wigs, while an allergy to shampoo is very rare. Contact dermatitis is occasionally induced therapeutically with dinitrochlorobenzene (DNCB) or diphenylcyclopropenone (DCP) in the treatment of alopecia areata (Fig. 19.10).



Fig. 19.9 Allergic contact dermatitis to hair dye

Contact dermatitis presents with an acute, subacute or chronic eczema. It may be localized to the scalp and adjacent areas, or spread to involve other parts of the head and neck.

19.6.6 Pathology

The histological features of acute contact dermatitis include spongiosis, intracytoplasmic vacuolation, and nuclear pyknosis. Spongiosis in irritant contact dermatitis is more pronounced. Chronic contact dermatitis can display psoriasiform features of hyperkeratosis with areas of parakeratosis, elongation of rete ridges, and epidermal acanthosis.

19.6.7 Differential Diagnosis

Contact dermatitis should be distinguished from atopic dermatitis, psoriasis and seborrheic dermatitis. A complete history of substances used for the hair or scalp should be taken. History of atopy and distribution of dermatosis should elucidate the final diagnosis as well. In cases where the clinical suspicion of an allergic contact dermatitis is high or where the patient is refractory to treatment, patch testing should be performed to a



Fig. 19.10 Allergic contact dermatitis to diphencyprone used in the treatment of alopecia areata

Table 19.6 Treatment of contact dermatitis

Treatment	Level of evidence
Topical corticosteroids	2
Topical tacrolimus	2
Systemic corticosteroids	5

battery of chemical antigens. Irritant contact dermatitis does not show up on patch testing but a usage test with the suspected irritant may be indicated in difficult cases.

19.6.8 Treatment

Contact dermatitis is treated in the short term with topical corticosteroids [22] (Table 19.6). Topical tacrolimus can be used as well [2]. In severe cases, systemic corticosteroids may be used. Irritation of the scalp can be minimized by using a mild shampoo and avoiding all hairdressing procedures for at least a month following clinical recovery. If allergens are identified on patch testing, the patient should be advised to avoid these in future.

19.7 Pustular Conditions of the Scalp

Synonyms
pimples, folliculitis, acne

Key Features

- Scalp pustules can be inflammatory or infective.
- Pustular conditions affecting the scalp can result in destruction of the hair follicle with consequent alopecia and scarring.
- Treatment involves using a tetracycline antibiotic and an anti-yeast or tar shampoo.

19.7.1 Introduction

Follicular pustules on the scalp can occur with or without destruction of the hair follicles and scarring.

19.7.2 History

A number of distinct pustular conditions of the scalp have been described; however, it is unclear whether these represent distinct entities or belong to the same family.

19.7.3 Epidemiology

Pustules on the scalp are very common, and almost everyone will develop one or more crops at some time in their life.

19.7.4 Pathogenesis

Follicular pustules may be infectious or inflammatory. Common infectious organisms include staphylococci bacteria and pityrosporum yeasts. Non-infectious inflammatory non-destructive folliculitis can be seen with acne vulgaris, eosinophilic folliculitis, and seborrheic dermatitis. As the pustules are frequently pruritic and excoriated, secondary infection may occur. Destructive folliculitis can be a feature of acne necrotica, folliculitis decalvans, and dissecting cellulitis of the scalp.

19.7.5 Clinical Features

This condition often starts off as a pruritic or slightly painful follicular papule that may occur anywhere in the scalp, most typically on the vertex. These are often excoriated before slowly resolving over 1–2 weeks. Lesions may occur singly or in crops. Patients may have acne or folliculitis elsewhere in the body.

In acne necrotica, the lesions most commonly occur around the frontal hair line, presenting as a papule that pustulates and becomes centrally umbilicated. The lesion later develops central necrosis and ulceration that eventually crusts over (Fig. 19.11). The crust is eventu-



Fig. 19.11 Scalp pustule in acne necrotica

ally shed to leave a classical varioliform scar. Patches of cicatricial alopecia may result.

19.7.6 Pathology

Histology reveals an acute inflammatory infiltrate in the follicular infundibulum and beneath the adjacent stratum corneum. Disruption of the hair follicle produces a dermal inflammatory infiltrate as well. Colonies of bacteria or yeast may be seen in the follicle. In acne necrotica, the folliculitis is accompanied by necrosis of the hair follicles and a predominantly lymphocytic perivascular and periappendageal inflammatory infiltrate.

Bacterial cultures may grow *Staphylococcus* sp., while a Gram stain of the biopsy tissue may reveal Gram-positive pleomorphic rods of *Propionibacterium acnes*.

19.7.7 Treatment

Tetracyclines used for acne vulgaris will usually induce remission and are often combined with anti-yeast or tar shampoo (Table 19.7). Maintenance therapy is usually required with long-term antibiotic therapy and medicated shampoos. Resistant cases may benefit from isotretinoin [31] but there are insufficient numbers of patients who have been treated with this drug to make firm conclusions about its efficacy.

Table 19.7 Treatment of pustular conditions of the skin

Treatment	Level of evidence
Oral tetracycline	5
Oral isotretinoin	5

19.8 Pruritus and Burning of the Scalp

Synonyms
trichodynia, scalp dysesthesia

Key Features

- Pruritus can be a troubling symptom that may be associated with an inflammatory or infective condition.
- Thorough history and examination of the scalp is necessary to exclude clinical signs of an underlying condition.
- In the absence of a diagnostic explanation, a somatization disorder such as depression should be thought of.

19.8.1 Introduction

Pruritus refers to itch. This symptom may be associated with an inflammatory condition of the scalp or with an apparently normal scalp. Conditions that are not usually thought of as pruritic dermatoses such as pityriasis capitis, psoriasis, and androgenetic alopecia can occasionally be accompanied with severe pruritus.

19.8.2 Epidemiology

An itchy scalp is a common complaint, while a burning scalp is seen less frequently.

19.8.3 Pathogenesis

The mechanism of scalp pruritus is no different to pruritus elsewhere in the skin and is mediated by a number of chemicals including histamine, bradykinin, prostaglandins, and various neurotransmitters. The pathogenesis of burning scalp is unknown but may be related to the aberrant expression of substance P. Very occasionally scalp dysesthesia accompanies early androgenetic alopecia.

19.8.4 Clinical Features and Differential Diagnosis

Signs of underlying dermatosis may be absent or subtle, and close inspection of the entire scalp may be necessary in detecting this. Manifestations of scratching such as broken hair shafts, linear excoriations, prurigo nodules or lichen simplex may also be identified (Fig. 19.12). Broken shafts due to rubbing are most noticeable over the parietal and temporal regions while lichen simplex is seen most frequently in the nuchal area, where it may mimic psoriasis.

Pityriasis capitis and androgenetic alopecia may occasionally produce severe pruritus especially in patients who are under stress or who are depressed, but other causes should be excluded before accepting either as the sole cause.



Fig. 19.12 Nodular prurigo with excoriation

Conditions that can produce itch with few or no objective signs include urticaria, allergic contact dermatitis, endogenous atopic dermatitis, *Pityrosporum* folliculitis, acne necrotica, dermatitis herpetiformis, and pediculosis. This list is incomplete but serves as a useful starting point for dealing with patients with an itchy scalp and no obvious cause.

In allergic contact dermatitis, there are often clues in the history. Patch testing may identify the allergen. If avoidance of the allergen cures the itch, then it is reasonable to assume that was the cause. Urticaria may also produce very few clinical signs initially, but eventually most people will develop wheals elsewhere in the body. Pustules can be easily missed without a diligent search through the entire scalp. Finding even one or two pustules may enable a diagnosis of *Pityrosporum* folliculitis or acne necrotica to be made. Both these conditions can produce intense focal itching.

If the patient only has a few lice or nits then it is possible to miss this diagnosis. A careful search of the scalp may find some of these arthropods and explain the generalized itch. Dermatitis herpetiformis may present on the scalp and produce a severe itch. The only sign may be a few excoriations with or without vesicles.

In the absence of an obvious cause of the itch, and after thorough examination of the scalp looking for pustules, vesicles and inflammatory papules, the rest of the skin should be examined for cutaneous disorders such as atopic dermatitis, psoriasis, and dermatitis herpetiformis. Possible contact allergens should be sought in the history and an inquiry should be made into recent stresses coincident with the onset of the pruritus. Depression may somatize as scalp itch, in which case it is often described as being present all day and all night. Early morning wakening and loss of appetite may be important clues to the diagnosis.

Frequently no cause is found for the itch and a diagnosis of idiopathic pruritus capitis is tentatively made. The patient is then treated empirically and is regularly re-evaluated for a diagnosis that may not have been initially apparent.

19.8.5 Treatment

In the presence of a dermatosis, that condition should be treated on its merits. Itch usually responds to tar shampoos, however steroid scalp lotions may also be required. Sedatives and antidepressant medications may be used if there is an element of associated depression or anxiety. Topical capsaicin has been used empirically for scalp pain without success. In cases where the scalp symptoms are accompanied by androgenetic alopecia, occasionally treatment with either finasteride in men or oral antiandrogens in women results in resolution of the dysesthesia.

Summary for the Clinician

Diseases of the scalp can present with a myriad of symptoms and signs which includes pruritus, burning, scale, discharge, and hair loss. Occasionally it can be difficult to distinguish between these diseases based on the clinical features. A careful examination of the scalp and the rest of the body needs to be carried out in this situation, as well as appropriate investigations including skin scrapings and a biopsy of the affected area for histopathology. A definitive diagnosis will guide the management of the disorder in question. The treatment of some of these disorders may overlap, for example the use of topical corticosteroid lotions and tar shampoos for both psoriasis and atopic dermatitis of the scalp; therefore, distinguishing between the two may not be absolutely essential.

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Chapter 20

Psychocutaneous Disorders of Hair and Scalp

20

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Synonyms

psychophysiological disorders, primary psychiatric disorders, cutaneous sensory disorders, secondary psychiatric disorders, anxiety disorder, neurotic scalp excoriations, trichotillomania, factitial dermatitis of the scalp, scalp dysesthesia, psychogenic pseudoeffluvium, delusion of parasitosis

Key Features

- Many patients with a hair or scalp disorder have psychological issues associated with their chief complaint.
- To handle these cases of imaginary hair loss, abnormal scalp sensations, or self-induced injury to the hair or scalp effectively, the dermatologist must be capable of classifying and diagnosing psychocutaneous disorders.
- There are two ways to classify psychocutaneous cases: first, by the category of the dermatologic presentation; and, second, by the nature of the underlying psychopathologic condition.
- If the dermatologist considers treating these patients with psychopharmacologic agents, the selection of appropriate agents is dictated by the nature of the underlying psychopathologies.
- Finally, the best way to alleviate the emotional distress caused by a hair disorder is to effectively treat it.

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20.1 Introduction

Many patients with a hair or scalp disorder have psychological issues associated with their chief complaint. Few dermatologic complaints carry as many emotional overtones as those related to the condition of the hair. Then again, patients who are convinced they are going bald may not show any evidence of hair loss, or abnormal scalp sensations reported by the patient and hair or scalp defects cannot be related to a specific dermatologic disease. To handle these cases of imaginary hair loss, abnormal scalp sensations, and self-induced injury to the hair or scalp effectively, the dermatologist must be able to classify and diagnose psychocutaneous disorders and select the appropriate class of psychopharmacologic agent as indicated. It is the objective of this chapter to give a comprehensive and practical approach to both the diagnostic and therapeutic aspects of psychodermatologic conditions affecting the hair and scalp.

20.2 History

In a monograph entitled *"The Unconscious Significance of Hair"* Charles Berg (1950) reviewed the anthropological literature on hair, and emphasized its significance in many rituals in a variety of primitive cultures. He pointed out that hair has, in modern Man, practically no other significance except as a sexual symbol, and claimed that there is no normal individual without some degree of hair fetishism. Hair has been recognized to have two perceived symbolic meanings in a spiritual context: shaven hair is a symbol of celibacy and chastity; in contrast uncut hair is seen as a withdrawal from worldly concern and vanities. Sometimes long hair represents a concession to religion, such as in the Sikh religion and for the Rastafarians, although today it has also become a symbol of identity. In 1971, Opler, in discussing long hair in males in the United States, felt that hair style is a reflection of group attitudes culturally defined rather than of individual feelings. Investigations of male students classified as "deviant" with regard to their hair length revealed that they assigned a high value to independence and less value to recognition and conformity. In contrast, the importance placed on short hair by the armed forces of many countries reinforces the popular association of short hair with authority and discipline.

Self-inflicted lesions, excluding injuries produced accidentally through physical or chemical cosmetic procedures, are aberrant. The most frequent form of deliberate harm to the scalp consists of plucking the hair. Hallopeau is given credit for describing the clinical syndrome of hair loss resulting from the repetitive pulling and plucking of one's own hair; in 1889 he termed this syndrome trichotillomania. In 1902 Raymond referred to this syndrome as *tic d'épilation,* Sutton (in 1916) as *trichorrhexomania,* and Sabouraud (in 1936) as idiopathic trichoclasia. Besnier, in discussing Hallopeau's case, noted associated trichophagy in an affected infant. Other forms of self-inflicted injuries of the scalp are less common. They may result from delusions of parasitosis, first described in 1938 by Ekbom as neurotic excoriations or factitial dermatitis (Münchhausens syndrome).

Finally, in 1965 Meador introduced the concept of "non-disease" and pointed out that the absence of diagnostic signs and symptoms need not imply the absence

of a significant disorder. In this context, scalp symptoms have been recognized to be more common in women and are chiefly of excess hair loss and scalp dysesthesia. From the psychiatric point of view these patients do not consist of a uniform group. Most have been recognized to suffer from a disturbed body image, and many to be depressed. Depressive illness may be accompanied by alopecia. Although the patient may tend to blame the alopecia for the depression, a detailed history often reveals that the emotional and hair changes developed in parallel. There remains controversy as to the relationship between depression, stress, and hair loss, nevertheless the distress caused by the alopecia is currently believed to contribute to its perpetuation.

20.3 Epidemiology

It is a common experience among dermatologists that significant numbers of their patients have psychological overlays to their chief complaints. This particularly holds true for complaints related to conditions of the hair and scalp. The exact incidence in any particular dermatologic practice most likely depends on the dermatologist's interest; however, even for those dermatologists who are not specially interested in the psychological aspects of dermatologic disease, some patients have such overt psychopathologic conditions, such as trichotillomania, factitial dermatitis, or delusions of parasitosis, that even the least psychologically minded dermatologist feels obliged somehow to address the psychological issues. Ideally, this would be accomplished simply through referral of the patient to a mental health professional; in reality, the majority of psychodermatologic patients are reluctant to be referred to a psychiatrist. Many lack the insight regarding the psychological contribution to their dermatologic complaints; others fear the social stigmatization of coming under the care of a psychiatrist.

20.4 Categorizing Psychocutaneous Disorders

The dermatologist is often the physician designated by the patient to handle their chief complaint, even if the main disorder is a psychological one. Therefore, it is essential for dermatologists dealing with such patients to expand their clinical acumen and therapeutic armamentarium to effectively handle the psychodermatologic cases in their practice. To accomplish this goal the following steps are required [28]:

- Learn to classify and diagnose psychodermatologic disorders [25, 28]. Because so many different types of conditions lie in between the fields of dermatology and psychiatry, it is paramount to have classification systems that will help clinicians understand what they are dealing with. There are two ways to classify psychocutaneous cases: first, by the category of the dermatologic presentation, e.g., neurotic excoriation, and, second, by the nature of the underlying psychopathologic condition, e.g., depressive disorder, generalized anxiety disorder, or obsessive-compulsive disorder.
- Become familiar with the various therapeutic options available, both non-pharmacologic and psychopharmacologic.
- Recognize the limits of what can be accomplished in a dermatologic practice: typically, a dermatologist does not have the time, training, or inclination necessary to administer most non-pharmacologic approaches. If a dermatologist seriously considers the challenge of treating these patients with psychopharmacologic agents, the selection of appropriate agents is dictated by the nature of the underlying psychopathologies that need to be treated. In order to prescribe effectively and safely for these patients, the dermatologist must have a basic understanding of the pharmacology of psychotropic agents [26].
- Optimize working relationships with psychiatrists, since dermatologists and psychiatrists tend to have different perspectives when analyzing a clinical situation, different styles of communication, and different approaches to management.

Most psychocutaneous conditions of the hair and scalp can be grouped into the following four categories [28]:

- *Psychophysiological disorders,* in which the scalp disorder is exacerbated by emotional factors, e.g., hyperhidrosis, atopic dermatitis, psoriasis, and seborrheic dermatitis of the scalp.
- *Primary psychiatric disorders,* in which there is no real skin condition, but all symptoms are either self-induced or delusional, e.g., trichotillomania, neurotic excoriations, factitial dermatitis, delusion of parasitosis, or psychogenic pseudoeffluvium.
- *Cutaneous sensory disorders,* in which the patient has various abnormal sensations of the scalp with no primary dermatologic lesions and no diagnosable internal medical condition responsible for the sensations.

- *Secondary psychiatric disorders,* in which patients develop emotional problems as a result of hair loss, usually as a consequence of disfigurement.

20.5 Underlying Psychopathologic Conditions

20.5.1 Psychophysiological Disorders

Psychophysiological disorders is the term used for psychocutaneous cases in which specific dermatologic skin disorders, such as psoriasis and eczema, are exacerbated by emotional stress in a significant proportion of patients. Examples affecting the scalp include hyperhidrosis, atopic dermatitis, psoriasis, and seborrheic dermatitis. In each of these conditions, one comes across two types of patients: those who experience a close chronologic association between stressful experiences and exacerbation of their dermatologic condition, and those for whom the emotional state seems not to influence the natural course of their disease. These two groups are referred to as "stress responders" and "non-stress responders," respectively. The relative proportion of stress responders versus non-stress responders varies among the different psychophysiological conditions. For example, a study conducted by Griesemer involving a large number of subjects from the Harvard health care system in Boston, Massachusetts, determined the proportion with emotional trigger to be 100% in patients with hyperhidrosis, 70% in those with atopic dermatitis, 62% with psoriasis, and 41% with seborrheic dermatitis [20].

This category also includes the *psychosomatic disorders* – the physical symptomatic representation of unsolved emotional conflicts [38]. For classification we may consider the different levels of psychosomatic disorder. The first is physiological, and includes bodily sensations in response to emotional shifts, great or small. In health these bodily sensations make little or no impact on consciousness. At the second level, the person becomes more or less constantly aware of the somatic sensations, which are of purely functional nature at this time point, attempts to analyze them, and becomes anxious that they might signify some serious organic disease. The third level is the important one, at which internal somatic medicine and psychiatry meet. The organs and parts of the body have enormous elasticity and rebound, but if the underlying emotional distress is too prolonged, they supposedly lose their elasticity, no longer being able to cope, and finally protest in terms of the psychosomatic organ lesion or organ pathology. It has long been recognized that psychosomatic factors play a role in dermatologic disease. It has been hypothesized that an organ system is vulnerable to psychosomatic ailments when several etiologic factors are operable. These factors include: emotional factors mediated by the central nervous system; intrapsychic processes such as self-concept, identity, or eroticism; specific correlations between the emotional drive and the target organ, i.e., social values and standards linked with the organ system; and a constitutional vulnerability of the target organ. For example, persistent telogen effluvium in women that cannot be explained otherwise may be related to marital difficulties. Here the constitutional vulnerability of the target organ would be androgenetic alopecia, and the specific correlation would be that between a full head of hair and male recognition of female desirability and sexual attractiveness and their loss.

20.5.2 Primary Psychiatric Disorders

The term primary psychiatric disorders refers to cases in which there is no real skin condition. Everything that is seen on the scalp is self-induced, and there are no objective signs of other complaints relating to the condition of the hair and scalp. This category includes conditions such as trichotillomania, neurotic excoriations, factitial dermatitis, delusions of parasitosis, and psychogenic pseudoeffluvium.

Since the clinical presentations are quite stereotypic, but the underlying psychopathology varies, a critical step in psychodermatology is to try to ascertain the nature of the underlying psychopathologic condition. Any one of the numerous psychopathologies listed in the *Diagnostic and Statistical Manual of Mental disorders,* 4th edition (DSM IV) and in the *International Statistical Classification of Diseases and Health-related Problems,* 10th edition (ICD-10) can be presented by these patients. However, in general, where the patient's psychopathologic conditions are so obvious that it would be difficult even for a non-psychiatrist to ignore them, one of the following four types of underlying psychopathology is present:

- Generalized anxiety disorder (DSM-IV 300.02, ICD-10 F41.1)
- Depressive disorder (DSM-IV 300.4, ICD-10 F34.1)
- Delusional disorder (DSM-IV 297.1, ICD-10 F22.0)
- Obsessive-compulsive disorder (DSM-IV 300.3, ICD-10 F42.x).

20.5.2.1 Generalized Anxiety Disorder

Generalized anxiety disorder is characterized by a sustained, increased free floating anxiety, which is not orientated towards a certain object or situation. It expresses itself in the form of anxious expectations and enhanced alertness, combined with hypertension and, as a physiological correlate, autonomic hyperreactivity. Subjective symptoms include feelings of restlessness, irritability, feeling "on edge," tension, dizziness, agitation, and an inability to relax. These are frequently associated with physiological correlates such as muscle tension, sweating, shortness of breath, dry mouth, palpitations, abdominal complaints, and frequent urination. When patients with psychophysiological disorders complain that they are "stressed," they are usually referring to an underlying sense of anxiety. The uninhibited breakthroughs of tremendous anxiety show that the anxiety defense mechanisms have failed in the affected individuals. The causes of anxiety are repressed, but the ongoing arousal and fear are overwhelming. The patient's appearance is clinging and helpless. The patients signify a strong demand to be guided and assisted in their surroundings. The fixation towards fear of love deprivation may lead to attachments to strong "father figures," e.g., a physician, and strong emotional reactions on parting situations: a change of physician can cause severe separation anxiety and may therefore seem unbearable.

Cutaneous expressions on the scalp of generalized anxiety disorder (DSM-IV 300.02, ICD-10 F41.1) may be:

- neurotic excoriations of the scalp
- scalp dysesthesia.

20.5.2.2 Depressive Disorder

In a *depressive disorder* the affected individual suffers from the symptoms of a depressive syndrome, which may be interspersed with shorter or longer periods of normal mood. Depression is characterized by subjective symptoms, such as depressed mood, crying spells, anhedonia (inability to experience pleasure), a sense of helplessness, hopelessness and worthlessness, excessive guilt, and suicidal ideation. Frequently associated physiological correlates are psychomotor retardation or agitation, insomnia or hypersomnia, loss of appetite or hyperphagia, and, especially in older patients, complaints of constipation.

In a *depressive character disorder,* affected individuals appear humble, unambitious, and sacrificing. They have high self-expectations and avoid close approaches from others; they would rather give up their own intentions and become subordinate to others. Usually there are co-existing wishes of dependency, that others shall acknowledge the sacrifice, and turn their attention and love to them. In others this may provoke an aggressive defense mechanism, which may appear as a hostile dissociation. These mismatched expectations mainly affect the patient's partnerships, when self-sacrifice and the excessive demand of love become overbearing.

Cutaneous expressions on the scalp of depressive disorder (DSM-IV 300.4, ICD-10 F34.1) may be:

- neurotic excoriations of the scalp
- scalp dysesthesia
- psychogenic pseudoeffluvium.

20.5.2.3 Delusional Disorder

The presence of delusion defines psychosis. A *delusion* is a false idea on which the patient is absolutely fixed. By definition, delusional patients have no insight, and others cannot talk them out of their belief system. The type of psychotic patient most often seen by the dermatologist is not the schizophrenic, but the patient with monosymptomatic hypochondriacal psychosis.

Monosymptomatic hypochondriacal psychosis is characterized by a delusional ideation held by a patient that revolves around one particular hypochondriacal concern, while with schizophrenia many other mental functions become compromised, besides the presence of delusional ideation.

A *delusion* is deemed to be a basic psychotic phenomenon, in which the objective falseness and impossibility of the delusional content are usually easy to realize. Delusional convictions are not simple misbeliefs, they are constitutions of an abnormal mind that refer to the individual's cognitive experiences of his or her environment – their ego–environment relationship. Delusions are not voluntarily invented by the patients: they are caused by psychotic experiences. From the psychodynamic point of view, a delusional disorder is a special consequence of abnormal self-development. The delusion derives from the patient's desire to be in a safe place, away from the tension caused by the brittleness and contradictoriness of the patient's ego–environment relationship. The subjective certainty of the delusion's content causes its incorrectability: patients consistently keep their convictions, without considering their incompatibility with reality. Neither contrary experiences, nor logical arguing can influence them.

Psychocutaneous manifestations on the scalp of delusional disorder (DSM-IV 297.1, ICD-10 F22.0) may be:

- delusions of parasitosis
- psychogenic pseudoeffluvium.

20.5.2.4 Obsessive-Compulsive Disorder

Obsessive-compulsive symptoms may be seen across the whole spectrum of psychopathology. In early childhood they may occur as a temporary phenomenon in response to stress or anxiety, e.g., trichotillomania; they may occur as a psychoneurotic symptom in a person with an obsessive-compulsive personality configuration, e.g., onychophagia or acne excorié; they may occur as a feature of the obsessive-compulsive disorder (for definition see below); or they may also occur in patients with psychosis.

Individuals with an obsessive-compulsive personality configuration are rigid, perfectionistic, and indecisive for fear of making a mistake; they lack self-confidence, are sensitive to criticism, and are socially reserved. Perhaps most importantly, they have profound difficulty in handling anger and aggression, which sometimes is explosive and at other times is displaced into self-destructive picking of the skin rather than being expressed directly in a modulated fashion.

The essential feature of obsessive-compulsive disorder required for diagnosis is recurrent obsessions or compulsions that are severe enough to be time-consuming or cause impairment in relationships, employment, school, or social activities. An *obsession* is a persistent idea, thought, impulse, or image that intrudes into a person's consciousness uncontrollably and causes distress, anxiety, and often feelings of shame. By definition, patients suffering from obsessive-compulsive disorder have insight into their condition whereas delusional patients do not. The individual with obsessive-compulsive disorder realizes that the obsession is inappropriate and irrational, but cannot resist. The obsessional concerns often lead to compulsive acts. *Compulsions* are repetitive, stereotyped motor acts, often ritualized, and designed to reduce intolerable anxiety or distress.

Obsessions may involve themes of aggression (harming the self or others), contamination (dirt, germs, body secretions), sex (forbidden thoughts or impulses), religion (concern with blasphemy or sacrilege), or somatic concerns.

Psychocutaneous manifestations on the scalp of obsessive-compulsive disorder (DSM-IV 300.3, ICD-10 F42.x) may be:

- trichotillomania
- neurotic excoriations of the scalp
- factitial dermatitis of the scalp

20.5.3 Cutaneous Sensory Disorders

Some patients only present with a cutaneous sensory complaint such as itching, burning, stinging, or other disagreeable sensations without any diagnosable dermatologic, neurologic, or medical diagnosis. Patients with chronic cutaneous sensory disturbance of unknown etiology can be divided into those with diagnosable psychiatric findings, such as a depression or anxiety, and those with no diagnosable psychiatric findings [29]. The latter patients have been termed to be suffering from *somatoform pain disorder.*

It represents one of four major *somatoform disorders:*

- Conversion disorder, also known as hysteria (DSM-IV 300.11, ICD-10 F44.xx)
- Hypochondriacal disorder and body dysmorphic disorder (DSM-IV 300.7, ICD-10 F45.2)
- Somatization disorder, also known as Briquet's syndrome (DSM-IV 300.81, ICD-10 F45.0)
- Somatoform pain disorder (DSM-IV 307.xx, ICD-10 F45.4).

In dermatology the somatoform disorders consist of a heterogeneous pattern of differing clinical presentations based on a comparable emotional disorder, the characteristic of which is repeated presentation of physical symptoms in combination with a stubborn demand for medical examination, despite repeated negative results, and the physician's assurance that the symptoms have no physical basis. The term *dermatologic non-disease* has also been coined for this disorder [5].

20.5.3.1 Conversion Disorder

Conversion disorder is characterized by the loss of a bodily function. It is involuntary, and diagnostic testing does not show a somatic cause for the dysfunction. The patient with conversion disorder confronts an acute stressor, which creates a psychic conflict and the physical symptoms serve as the resolution of the conflict, while the patient may be unaware of the stressor. Conflicts or other stressors that precede the onset or worsening of the symptoms suggest that psychological factors are related to it. The disorder may be best thought of as disturbances of illness perception or need. They are paradigms of mind–body interactions and of the critical role that mental factors play in the production of illness. Again, the loss of function may symbolize the underlying conflict associated with it. Psychodynamic theory interprets the cause of the symptoms as a defense mechanism that absorbs and neutralizes the anxiety generated by an unacceptable impulse or wish. The patient doesn't consciously feign the symptoms for material gain or to occupy the sick role.

Cutaneous expressions on the scalp of conversion disorder (DSM-IV 300.11, ICD-10 F44.xx) may be:

- scalp dysesthesia.

20.5.3.2 Hypochondriacal Disorder and Body Dysmorphic Disorder

Unlike conversion disorder, where the affected individual perceives a functional disorder and simply uses it to escape from uncomfortable situations, the patient with *hypochondriacal disorder* has no real illness, but is overly obsessed over normal bodily functions. They read into the sensations of these normal bodily functions the presence of a feared illness. Because of misinterpreting bodily symptoms, they become preoccupied with ideas or fears of having a serious illness, while appropriate medical investigation and reassurance do not relieve these ideas. These ideas cause distress that is clinically important or impairs work, social or personal functioning. They are not delusional (as in delusional disorder) and are not restricted to concern about appearance (as in body dysmorphic disorder: see below). Hypochondriacal disorder usually develops in middle age or later and tends to run a chronic course. Patients typically seek many tests and much reassurance from their doctor.

Probably the more important group of problem patients for the dermatologist in practice is that with *body dysmorphic disorder* or "dysmorphophobia" (a term that is incorrect, since we are not dealing with a phobic disorder) [7]. It is classified together with hypochondriacal disorder, though this classification will probably be abandoned in future in favor of a new class of its own. This disorder tends to occur in younger adults. The patient becomes preoccupied with a non-existent or minimal cosmetic defect and persistently seeks medical attention to correct it. Cases of body dysmorphic disorder can range from relatively mild to very severe. The patient is preoccupied with an imagined defect of appearance or is excessively concerned about a slight physical anomaly. This preoccupation causes clinically important distress or impairs work, social or personal functioning. Another term used for body dysmorphic syndrome is *Thersites complex* (named after Thersites who was the ugliest soldier in Odysseus' army, according to Homer). One of various theories attempting to make the onset of body dysmorphic disorder understandable is the "self-discrepancy theory," in which affected patients present conflicting self-beliefs with discrepancies between their actual and desired self. Patients have an unrealistic ideal as to how they should look. Media-induced factors are considered to predispose to body dysmorphic disorder by establishing role models for beauty and attractiveness. Probably a variant of body dysmorphic disorder is the more recently described *Dorian Gray syndrome* [3] (named after an Oscar Wilde novel, in which the protagonist, a beautiful young aesthete, exclaims in front of his portrait: "Why should it keep what I must lose? Every moment that passes takes something from me, and gives something to it. Oh, if it were only the other way! If the picture could change, and I could be always what I am now!" [58]), in which patients wish to remain forever young and seek lifestyle drugs and surgery to deter the natural aging process.

Psychocutaneous manifestation on the scalp of hypochondriacal disorder and body dysmorphic disorder (DSM-IV 300.7, ICD-10 F45.2) may be:

- psychogenic pseudoeffluvium.

20.5.3.3 Somatization Disorder

Somatization disorder presents with a pattern of recurrent, multiple somatic complaints that do not have an organic basis [48]. Starting before the age of 30, the patient has usually had many physical complaints occurring over several years and sought treatment for them, or the complaints have materially impaired social, work or personal functioning. Typically there is a combination of pain symptoms, related to different body sites or body functions, gastrointestinal symptoms, sexual dysfunction, and pseudoneurological symptoms. None of these is limited to pain (as in somatoform pain disorder: see below). Physical or laboratory investigations determine that each of the symptoms cannot be fully explained by a general medical condition or by substance abuse, including medications and drugs of abuse; or, if the patient does have a general medical condition, the impairment or complaint is greater than would be expected based on history, laboratory, and physical examinations.

In dermatology, environment-related physical complaints, the so-called *eco syndromes,* are noteworthy among the somatization disorders (DSM-IV 300.81, ICD-10 F45.0). The patients report multiple complaints in various organ systems, of which the purported cause is exposure to environmental toxins, without proof of any direct toxic causal relationship between exposure and symptomatology. Examples are the *multiple chemical sensitivity syndrome* and the *amalgam-related complaint syndrome.*

Occasionally, the complaint of hair loss is related to the amalgam in tooth fillings, and patients unnecessarily have all fillings removed and pay for expensive detoxification procedures.

20.5.3.4 Somatoform Pain Disorder

In *somatoform pain disorder,* by definition, pain is in the foreground. It is reported by the patient as clinically relevant, causes suffering and professional and/or social impairments, and cannot be adequately explained by either a somatic cause or another psychiatric disorder.

In dermatology, mainly regional cutaneous or mucosal dysesthesias occur. Depending on their localization, specific names for the conditions are available, such as glossodynia (tongue) and vulvodynia (vulva).

Psychocutaneous manifestation on the scalp of somatoform pain disorder (DSM-IV 307.xx, ICD-10 F45.4) may be:

- scalp dysesthesia.

20.5.4 Secondary Psychiatric Disorders

Secondary psychiatric disorders refer to the psychological impact of having a disfiguring dermatologic disease. Even though most patients with hair disorders experience significant psychological impact [4, 5, 11, 32], it is usually not of an intensity to qualify as a mental illness. Nevertheless, the impact that hair disorders have on body image significantly contributes to the overall impact on the patient's quality of life. If one appreciates the psychosocial impact of hair disease, there is no doubt that appropriate treatment frequently has a huge bearing on the patients' quality of life. The clinician should keep in mind that the distress the patient feels from having a hair disease can be handled both dermatologically and psychologically.

Some patients have difficulties adjusting to hair loss. As a result, the individual may have difficulty with his or her mood and behavior. From a psychopathological point of view, *adjustment disorders* may result from the stressful event of hair loss, depending on its acuity, extent, and prognosis. An adjustment disorder is a debilitating reaction to a stressful event or situation. These symptoms or behaviors are clinically significant as evidenced by either of the following: distress that is in excess of what would be expected, or significant impairment in social, occupational or educational functioning. Adjustment disorders subtypes include: adjustment disorder with depressed mood (DSM-IV 309.0, ICD-10 F43.20), adjustment disorder with anxiety (DSM-IV 309.24, ICD-10 F43.28), adjustment disorder with mixed anxiety and depressed mood (DSM-IV 309.28, ICD-10 F43.22), adjustment disorder with disturbance of conduct (DSM-IV 309.3, ICD-10 F43.24), and adjustment disorder with mixed disturbance of emotions and conduct (DSM-IV 309.4, ICD F43.25). Associated features may be somatic and/or sexual dysfunction, feelings of guilt and/or obsession.

Probably the best way to alleviate the emotional distress caused by hair disease is to eliminate the hair disease that is causing the problem. In other words, the intensity of the distress that the patient feels should be part of the clinician's formula in deciding how aggressively to treat the hair disease. For example, a decision to use or not to use finasteride in a patient with a borderline clinical state of androgenetic alopecia, or to recommend or not to recommend hair surgery to a patient with permanent alopecia, may hinge on the amount of distress the patient feels from the alopecia.

Besides being a sympathetic and concerned professional, a dermatologist may give a referral to a support organization such as the National Alopecia Areata Foundation. First, many of these support organizations specialize in providing educational materials to patients and their relatives so they have an opportunity to inform themselves with respect to the nature and prognosis of their hair problem. Second, being part of such an organization breaks the sense of isolation patients often feel. Finally, by learning more about different treatment options, there is less risk that the patients will prematurely give up on treatment in despair and resign themselves to having uncontrolled alopecia. Keeping up hope is critical in not losing a positive outlook, in spite of having a chronic or recurrent condition.

20.6 Dermatologic Presentations

20.6.1 Trichotillomania

Trichotillomania involves the repetitive, uncontrollable pulling of one's hair, resulting in noticeable hair loss [35]. The patient typically experiences an increasing sense of tension immediately before pulling out the hair or when attempting to resist the behavior, and a sense of pleasure, gratification, or relief when pulling out the hair. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. The disturbance is not better accounted for by another mental disorder and has been assigned its own classification (DSM-IV 312.39, ICD-10 F63.3).

Most commonly, scalp hairs are pulled, although hair may be pulled from any location. The resulting alopecia is incomplete and often asymmetrical (Fig. 20.1). When the hair is pulled in the centroparietal area of the scalp sparing the lateral margins and the nape of the neck, typically in female adolescents, a tonsural pattern may result, that has been termed *tonsure trichotillomania* [9, 44].

20.6.1.1 Pathogenesis

Trichotillomania represents a disorder of impulse control, not otherwise classified. It occurs six to seven times more frequently in children than in adults, before the

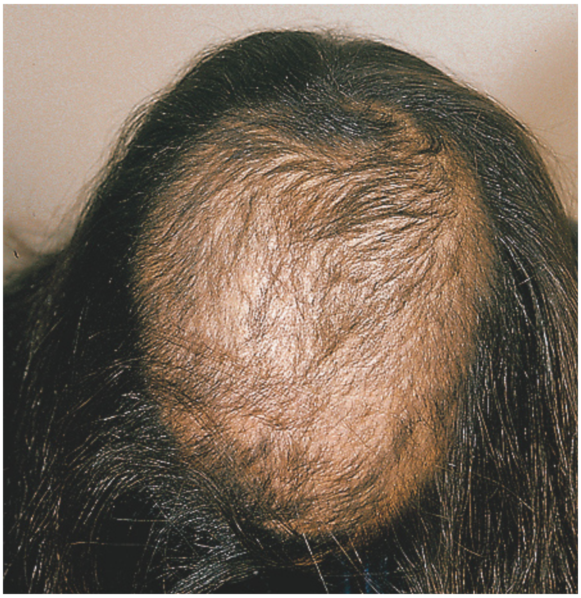


Fig. 20.1 Tonsure trichotillomania. From [54] with permission

age of 6 males predominate, thereafter females. The disorder usually begins between early childhood and adolescence. In many children, trichotillomania occurs in a climate of psychosocial stress in the family or at school, e.g., hospitalization of child or mother, sibling rivalry, inability to focus on activities and play in the younger child, and difficulties at school in the older child. Hair pulling and eating has also been observed in captive rhesus monkeys [43]. Hair pulling in children may result from a mild form of frustration, and soon becomes a habitual practice; hence, the French term "tic d'épilation" (*epilation tic*). From puberty onward, hair gains significance as a secondary sexual characteristic, thus denoting biological maturity and gender identity. Especially tonsure trichotillomania in the female adolescent is related to more severe pathologic psychodynamics, sometimes with disturbance of parent–child (especially mother) relationships and of the relationship with female sexual identity. A culture-bound form of hair pulling exists in India, where members of the Jain sect pull out their hair on the occasion of religious ceremonies to demonstrate detachment from physical pain [46].

20.6.1.2 Clinical Features

Trichotillomania typically presents with an incomplete ill-defined area of hair loss. In the affected areas there are different lengths of hair: short, longer, and normal. At times there will be an ill-defined linear configuration, which is very diagnostic. Most often the contralateral region of the scalp of right- or left-handed individuals is affected. If hairs are pulled out more easily than normal, or if regrowing hairs in children are non-pigmented it is not trichotillomania (but rather alopecia areata).

Associated features of trichotillomania may include: excoriations of the scalp, nail biting (*onychophagy*), and eating hairs (*trichophagy*) with the risk of gastrointestinal obstruction by a mass of hair (*trichobezoar*), a complication that has been termed the *Rapunzel syndrome* [10].

Parents seldom notice their child's behavior, and most of them do not believe that their child would pull out his or her own hair. Once the diagnosis is suspected, it is confirmed in the following way:

- With the parents out of the room, in a friendly way ask the youngster to show you how this is done. This immediately tells the patient that you know what is going on and often initiates the disclosure or demonstration of how it is done.
- If necessary, the next most simple way to prove the diagnosis is to perform a trichogram, which will typically show a significantly decreased telogen rate at the periphery of the area of hair loss (since the telogen hairs are more easily pulled out than the anagen hairs).
- Finally, do a biopsy. This cannot rule out the diagnosis, but, if present, the following histopathologic findings will confirm it: wavy, wrinkled, corkscrew-shaped hair shaft (*trichomalacia:* Fig. 20.2), the presence of many hairs in the catagen stage, and a lack of perifollicular inflammation (found in alopecia areata) [36, 55].

Children with trichophagy should be screened for iron deficiency as part of their evaluation, since the association of *pica* – an unusual craving for non-food items – and iron deficiency has been reported [34]. The compulsive oral behavior characteristically resolved with the oral administration of therapeutic doses of iron. It must be kept in mind though, that iron deficiency may either be a cause of trichophagy or result from gastrointestinal bleeding in the case of trichobezoar.

20.6.1.3 Differential Diagnosis

Some disorders have similar or even the same symptoms. The clinician, therefore, in his/her diagnostic attempt, has to differentiate against the following dermatologic and psychiatric disorders, which need to be ruled out to establish a precise diagnosis:

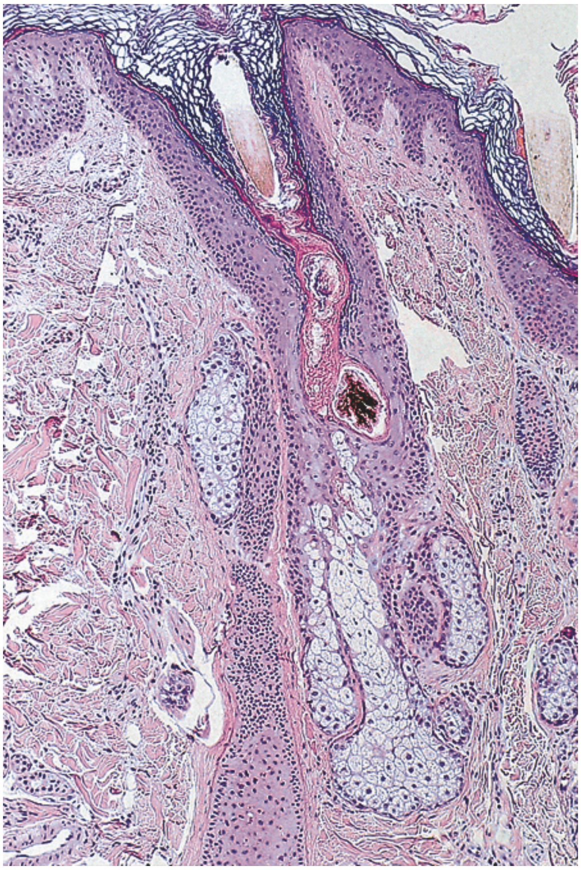


Fig. 20.2 Histology of a patient with trichotillomania showing the wavy, wrinkled, cork-screw-shaped hair shaft, called trichomalacia

- Alopecia areata: alopecia areata and trichotillomania present the most frequent causes of circumscribed hair loss in children. *Trichotillomania in connection with alopecia areata* has confused some observers. Either it may result from scratching at the site of alopecia areata that is symptomatic with pruritus, initiating a habit-forming behavior, or patients with a mental predisposition may artificially prolong the disfigurement as the hair on the bald patches of alopecia areata regrows. The aim of this may be to maintain gratification of dependency needs, which were previously met during the episode of alopecia areata [40, 55].
- Loose anagen hair.
- Tinea capitis presenting as "black dot" alopecia.
- Factitious disorder (Münchhausen syndrome).
- Traumatic alopecia due to child abuse (battered child) [52].

20

Besides the differential diagnosis of circumscribed hair loss, it is important to recognize the variants of trichotillomania:

- *Telogen mania* represents obsessive-compulsive fits of fierce hair brushing in women [24].
- *Trichophobia* denotes plucking of hair on the basis of the delusion of having to pull something out of the hair roots [28].
- *Trichotemnomania* is self-inflicted hair loss through deliberate cutting of hair. It represents a factitious disorder rather than an obsessive-compulsive disorder [2].
- *Trichoteiromania* is the term coined for breakage of hair by forcefully rubbing an area of the scalp; it is associated with a sensory disorder of the scalp [14].

20.6.1.4 Treatment

The primary treatment approach for trichotillomania is habit reversal combined with stress management and behavioral contracting. Parents can help by recognizing the problem in its early stages and getting involved in its treatment. Treatment may involve self-monitoring of hair-pulling episodes as well as the feelings and situations that are most likely to lead to hair pulling [1]. Youngsters are then systematically introduced to new behaviors; for example, squeezing a ball or tightening their fist whenever they feel the urge to pull at their hair. Relaxation training and other stress-reduction techniques may also be used, including reward charts that help track and monitor a child's progress with the added incentive of earning small rewards for continued progress. In addition, cognitive therapy is found to be effective.

The younger the patient, the smaller the percentage of cases referred to a psychiatrist; the rest are treated by the dermatologist who applies his or her own psychiatric knowledge (liaison psychiatry). A proper follow-up is required to establish whether improvement has actually occurred. When the symptom is present in adolescents or adults, competent help from a psychiatrist should be sought.

In a dermatologic setting, a pharmacologic approach may be most feasible for patients who refuse to be referred elsewhere. Basically, the same pharmacologic agents are used for the treatment of trichotillomania as for obsessive-compulsive disorder: the older tricyclic antidepressants imipramine [57] and clomipramine, and the newer selective serotonin reuptake inhibitors (SSRIs) fluoxetine [45], fluvoxamine, sertraline, and paroxetine. Physicians using SSRIs for treatment of patients with

obsessive-compulsive disorders or trichotillomania are cautioned that the duration of treatment is critical in determining adequate treatment. Improvement continues to occur when the drugs are taken beyond 8- or 12-week trials. A patient showing a partial response after 4–6 weeks would be expected to continue to improve during the following weeks. Cessation of pharmacotherapy results in a relapse the majority of patients. Despite success with SSRIs, patients with obsessive-compulsive disorders tend to respond to medication with only partial symptom reduction, suggesting that obsessive-compulsive disorders may be a neurobiological heterogeneous disorder that may require alternative treatment options in the individual patient. For example, successful treatment of five adult trichotillomania patients with a combination of the SSRI escitalopram with the anticonvulsant topiramat was recently reported [51].

20.6.1.5 Prognosis

With regard to prognosis, two types of trichotillomania are generally recognized: a temporary localized infant and childhood pattern with a good prognosis (epilation tic) [37], and a severe adult form typically occurring in young women, in which the affected area is more widespread and the prognosis is guarded (tonsure trichotillomania) [49].

20.6.2 Neurotic Scalp Excoriations

The term neurotic excoriations refers to patients with self-inflicted excoriations of the scalp in the absence of an underlying specific dermatologic disease condition. The etiology is varied, and psychiatrically, patients with neurotic excoriations are not a homogenous group, each requiring an individual therapeutic approach [15].

The condition may occur at any time from childhood to old age, with the most severe and recalcitrant cases reportedly starting in the third to fifth decade.

Because the patients, by definition, can inflict lesions only on those areas of the body that can be reached, and because patients tend to excoriate areas that are easily accessible, the clinical distribution of lesions besides the scalp can give a clue to the diagnosis. The lesions may affect the scalp in an isolated manner, or may be associated with excoriations of the face, and/or of the upper trunk and extensor aspects of the arms. The excoriations may be initiated by minor irregularities of the skin surface, such as a keratin plug, insect bite, acne papule (*acne excoriée*), or irritated hair follicle, or may start de novo. There is a decreased threshold for itch with tendency to habitual or neurotic scratching. Picking activity may start inadvertently as the hand comes across on an irregularity of the skin, or it may occur in an organized and ritualistic manner, sometimes using an auxiliary instrument, such as the point of a knife, etc. Tissue damage itself may again trigger itching, and the itch–scratch cycle may take on a life of its own. This activity typically takes place when the patient is unoccupied, and precipitating psychosocial stressors are usually present.

20.6.2.1 Pathogenesis

Neurotic excoriations occur across the spectrum of psychopathology. In mild and transient cases it may be a response to stress, particularly in the younger patient, such as examination stress (*thinker's itch*), mainly in someone with obsessive-compulsive personality traits. In the more severe and sustained cases, psychiatric evaluation may diagnose a generalized anxiety disorder (DSM-IV 300.02, ICD-10 F41.1), depression (DSM-IV 300.4, ICD-10 F34.1), or obsessive-compulsive disorder (DSM-IV 300.3, ICD-10 F42.x). Psychobiologically, obsessive-compulsive disorder is associated with decreased activity in serotonin-mediated neural pathways.

20.6.2.2 Clinical Features

The lesions are rather non-specific. Varying in size from a few millimeters to several centimeters in the well-developed case, lesions are seen in all stages of evolution, from small superficial saucerized excoriations through deep scooped-out skin defects (Fig. 20.3), to thickened hyperpigmented nodules and finally hypopigmented atrophic scars. Secondary bacterial infection may lead to regional lymphadenopathy. The histology is that of an excoriation with non-specific inflammatory changes. Microbiological studies may reveal secondary bacterial infection, usually with *Staphylococcus aureus.*

20.6.2.3 Differential Diagnosis

Since other dermatologic conditions can lead to similar lesions, clinicians must be careful not to make this diagnosis on the basis of the morphology of lesions alone. Specifically, pruritic skin conditions of dermatologic or other origin need to be excluded. Examples are: atopic dermatitis, acne miliaris necroticans, chronic cutaneous lupus erythematosus, pemphigus vulgaris, pemphigoid, parasitic infestation, neurologic disorders, and other psychiatric disorders, such as cocaine intoxication, delusions of parasitosis, and factitial dermatitis. Most importantly, one needs to confirm the diagnosis by ascer-



Fig. 20.3 Neurotic scalp excoriations. From [54] with permission

taining the presence of psychopathology through both clinical observation and direct patient questioning.

20.6.2.4 Treatment

Dermatologic treatment is symptomatic; psychiatric treatment includes psychological and psychopharmacologic approaches [16, 17].

Dermatologic treatment includes the prescription of non-irritating or "sensitive" shampoos, topical glucocorticoid-antibiotic cream preparations, and sedative antihistamines, such as hydroxyzine or doxepin [21], preferably given at nighttime. Cool compresses are soothing, provide hydration, and facilitate debridement of crusts. When followed by the application of an emollient, they reduce any contribution that xerosis makes to itching. When present, secondary bacterial infection must be treated appropriately, usually with a short course of oral antibiotics.

Psychiatric treatment includes non-pharmacologic and pharmacologic therapeutic options. In both, the choice of the appropriate technique or pharmacologic agent depends on the underlying mental disorder. Although behavioral modification, cognitive psychotherapy, psychodynamic psychotherapy, and an eclectic approach have met with variable success, many patients who present to the dermatologist are reluctant to agree to the psychiatric nature of their skin disorder and lack insight into the circumstances that trigger the drive to excoriate. Unless the patient is managed in a liaison clinic where dermatologists and psychiatrists can confer, it is the dermatologist who will take the responsibility for treatment.

If the patient is suffering from excessive stress, there are specific and non-specific approaches. Those individuals who can find specific, real-life solutions to the difficulties they report are the more fortunate ones. Many patients experience stress from work or home relationships for which there is no easy way out. For these patients, a non-specific solution to the stress can still be beneficial. Among the non-specific solutions to stress, there are non-pharmacologic and pharmacologic means. The non-pharmacologic means include: exercise, biofeedback, yoga, self-hypnosis, progressive relaxation, and other techniques learned in stress-management courses. Some patients do not have time to take stress-management courses, and others have special difficulty benefiting from this type of approach, for example those who are not psychologically minded. For these patients, cautious use of antianxiety agents may be an alternative. In general, there are two types of anxiolytics: a quick-acting benzodiazepine type that can be sedating and produce dependency, such as alprazolam, and a slow-acting non-benzodiazepine type that is not sedating and does not produce dependency, such as buspirone. Alprazolam differs from the older benzodiazepines such as diazepam and chlordiazepoxide because its half-life is short and predictable. Another advantage is that it has an antidepressant effect, whereas most other benzodiazepines generally have a depressant effect. Because of the possible risk of addiction with long-term use, the most prudent way of using alprazolam would be to restrict its use to 2–3 weeks. If the patient requires long-term therapy for anxiety, buspirone may be considered. However, it must be kept in mind that the effect of buspirone is usually not experienced by the patient for the first 2–4 weeks of treatment. Also, buspirone cannot be used on an "as needed" basis. If buspirone does not work for a patient with chronic anxiety disorder, an alternative would be the use of low-dose doxepin. Even though doxepin is a tricyclic antidepressant, in low doses, it has been compared to benzodiazepines in terms of its anxiolytic effects. Sometimes, also a low dose of a low-potency antipsychotic agent such as thioridazine can be used.

Although there are a number of non-pharmacologic treatment options for depression, most dermatologists have neither the time nor the training to execute these

treatment modalities. Nonetheless, it is advantageous to be conscious of these options, especially for those patients who agree to a referral to a mental health professional. Individual psychotherapy can be useful if there are definable psychological issues to be discussed, e.g., frustrations at work, a maladaptive style in interpersonal relationships, and the presence of maladaptive views of oneself, such as unrealistic expectations or fear of failure. Other patients have neurobiological predispositions to depression, and their depressive episodes may not be associated with any identifiable psychosocial difficulties. For these patients, the use of specific psychopharmacologic agents may in fact correct the primary cause of their depression. There are a number of antidepressants to choose from for treatment of depression pharmacologically. Among the tricyclic antidepressants, again doxepin is probably the most suitable for treatment of depressed patients with neurotic excoriations. If the patient cannot tolerate the sedative side-effect of doxepin, desipramine or one of the newer, non-tricyclic antidepressants such as fluoxetine, sertraline, and paroxetine are alternatives.

Finally, for the obsessive-compulsive patient with neurotic excoriations there are, once again, non-pharmacologic and pharmacologic therapeutic options. However, if the dermatologist were to follow a non-pharmacologic approach for patients who reject referral to a mental health professional, it would have to be a technique that is simple enough to perform in a dermatologic setting. One such technique is the invocation of a "1- or 5-minute rule," a simple behavioral technique to try to interrupt the progression from obsessive thoughts to compulsive behavior. The patient is asked to try to put an interval of 1–5 min between the occurrence of the obsessive thought and the execution of the compulsive behavior. Once the patient is successful in refraining for 1 min, the time is gradually increased to 5, 10, or even 15 min and, eventually, with such a long interruption between the obsessive thought and the compulsive behavior, one anticipates to break the natural progression from one to the other. In a dermatologic setting, the pharmacologic approach may be most feasible for patients who refuse to be referred elsewhere. Moreover, the recognition that serotonin pathways are involved and that the SSRI group of antidepressant agents reduces compulsive activity has made it more likely that the dermatologist will meet with success. Frequent short visits should be scheduled for supervision of the dermatologic regimen and for emotional support, and either clomipramine (an older antidepressant with extensive documentation about its anti-obsessive-compulsive efficacy in the medical literature) or one of the newer SSRIs (fluoxetine or fluvoxamine maleate) should be prescribed.

20.6.2.5 Prognosis

Untreated, the condition tends to persist, the severity fluctuating in parallel with psychosocial pressures. In general, cases of short duration have a more favorable prognosis. Dermatologic therapy, together with long-term intensive insight-oriented psychotherapy can lead to resolution in those patients who meet the criteria for such an approach. In others, topical measures, emotional support, and psychopharmacological therapy will bring about improvement, though exacerbations can be anticipated in relation to life's stresses.

20.6.3 Factitial Dermatitis of the Scalp

Factitial dermatitis (factitious disorder with physical symptoms: DSM-IV 300.19, ICD-10 F68.1) is a condition in which the patient creates lesions on the skin to satisfy a psychological need of which he or she is not consciously aware; usually a need to be taken care of by assuming the sick role [13, 18, 22, 30, 50]. Patients with factitious disorder or factitial dermatitis create the lesions for psychological reasons, and not for monetary or other discrete objectives as in the case of *malingering* (DSM-IV V65.2, ICD-10 Z76.5). Patients knowingly fake symptoms, but will deny any part in the process. They desire the sick role and may move from physician to physician in order to receive care. They are usually loners with an early childhood background of trauma and deprivation. They are unable to establish close interpersonal relationships and generally have severe personality disorders. Unlike malingerers, they follow through with medical procedures and are at risk for drug addiction and for the complications of multiple operations. In the more severe form known as *Münchhausen syndrome* or *laparotomophilia migrans,* a series of successive hospitalizations becomes a lifelong pattern.

20.6.3.1 Pathogenesis

Little is known about the etiology of factitious disorder. Besides the difficulties involved in making the diagnosis, the reluctance of these patients to undergo psychological testing and the heterogeneity in the details of cases published in the literature lie at the origin of this situation. Some clinicians have remarked that patients with factitious disorder often present traumatic events, particularly abuse and deprivation, and numerous hospitalizations in childhood, and as adults lack support from relatives and/or friends. The majority of patients suffer from borderline personality disorder. Because of emotional deficits in early life and a frequent history

of physical or sexual abuse, patients have failed to develop a stable body image with clearly defined physical and emotional boundaries. For these patients, the factitial lesions serve many purposes: the excitement and stimulation ease the sense of emptiness and isolation, and skin sensation defines boundaries and helps establish personal and sexual identity, whereas the sick role gratifies dependency needs. In all reported series, females outnumber male patients from 3:1 to 20:1; onset is highest in adolescence and early adulthood, and a remarkably high number of patients work, or have a close family member working, in the health care field.

20.6.3.2 Clinical Features

Factitial dermatitis of the scalp is only one aspect of the whole picture of factitious disease. The condition for which dermatologists are consulted often has already occasioned many visits to other physicians. The patient typically presents a bundle of normal investigative findings and a shopping bag filled with oral and topical medications. The lesions themselves are as varied as the different methods employed to create them; on the scalp there are usually ulcerations (Fig. 20.4) or areas of cut-off hair (*trichotemnomania*). They are bizarre in shape and distribution, and usually appear on normal skin [56]. Though the possibilities are limitless, consistent is a "hollow" history – a term that refers to the patient's vagueness and inability to give details of how the lesions evolved. Consistent also are the affect of both the patient and their family. Although the patient seems astonishingly unmoved by the lesions, the family is angry, accusatory, and critical of what they interpret as medical incompetence.



Fig. 20.4 Factitial dermatitis with superficial ulceration. From [54] with permission

20.6.3.3 Differential Diagnosis

A number of dermatologic, neurologic, and mental disorders may share similar symptoms. Clinically the considerations are determined by the morphology and cover the scope of clinical dermatology. Among the most important disorders affecting the scalp that have to be taken into consideration are: necrotizing herpes zoster (shingles), temporal arteritis, angiosarcoma, neurotrophic ulcerations of the scalp, and neurotic excoriations of the scalp.

20.6.3.4 Treatment

The essential and probably most difficult step is to secure an enduring and stable patient–physician relationship. For achieving this goal most clinicians advocate a non-confrontational strategy reframing the factitious manifestation as a "cry for help." An interesting approach is that of "contract conference." In this approach the psychiatrist emphasizes the need for the patient to express him/herself in the common language of difficult relationships, feelings, and problems in living instead of the (factitious) language of illness. After that the patient and clinician can focus their efforts on resolving those real problems. Once a stable relationship is installed the management of the disorder must be oriented to avoid unnecessary hospitalizations and medical procedures.

Another important issue in the management of this condition is recognition and adequate treatment of frequently associated disorders, such as personality disorders, depression, drug and/or alcohol abuse and dependency, etc.

Dermatologic treatment is symptomatic, and determined by the clinical presentation. The uses of occlusive dressings are a diagnostic tool rather than an effective therapeutic intervention, since success is only of a temporary nature. Because of the patient's intense emotional investment in their skin, it may be helpful to prescribe positive measures such as wet dressings, emollients, and other bland topicals to replace the prior destructive activity.

Some case reports focus on the use of pharmacological agents. A good response has been reported to the antipsychotic drug pimozide; other clinicians, because of the resemblance to the obsessive-compulsive disorder, advocate the use of clomipramine, or the SSRIs fluoxetine and fluvoxamine maleate.

20.6.3.5 Prognosis

In the vast majority of patients, the condition is chronic [47].

20.6.4 Delusions of Parasitosis

In delusions of parasitosis or *Ekbom's disease* [12] there is an unshakable conviction that the skin is infested by parasites [31, 59]. In the older literature, this condition is also described as "parasitophobia" or "acarophobia." However, the terms with "phobia" attached to them are misnomers, and should be omitted, because in classic phobia, patients are aware of the fact that their fearful reactions are both excessive and irrational, while in the case of delusions of parasitosis, the patient is truly convinced of the validity of his or her perceptions.

20.6.4.1 Pathogenesis

In dermatologic practice the type of delusional patient most frequently seen is the patient with a delusional ideation that revolves around only one particular hypochondriacal concern. These patients are said to suffer from monosymptomatic hypochondriacal psychosis. These patients are different from other psychotic patients, such as schizophrenics or patients with a major depression, since the latter have many deficits in mental functioning, which is not the case in patients with monosymptomatic hypochondriacal psychosis. Moreover, a delusional disorder appears to run distinct from schizophrenia and mood disorders, and does not appear to be a prodrome to either of these conditions. From a nosological point of view, delusions of parasitosis are classified as a delusional disorder of the somatic type, with predominantly somatic delusions (DSM-IV 297.1, ICD-10 F22.0).

20.6.4.2 Clinical Features

In the medical literature, the typical patient with delusions of parasitosis is reported to be a middle-aged woman, though there seems to be a bimodal distribution of age group. In addition to older women, this condition is frequently encountered in patients in their 20s and 30s of either sex who are at a lower socioeconomic status and who have a marginal existence in society, in work and in interpersonal relationships. Patients report cutaneous sensations such as crawling, biting and stinging, which they relate to their unshakable conviction that their skin is infested by parasites [42]. They often bring in bits of dry skin, debris, and other specimens to try to prove the existence of these "parasites" (Fig. 20.5). Sometimes secondary injury to the skin or infection such as cellulitis may result from excessive scratching or the attempt to remove the "parasites" from the skin.

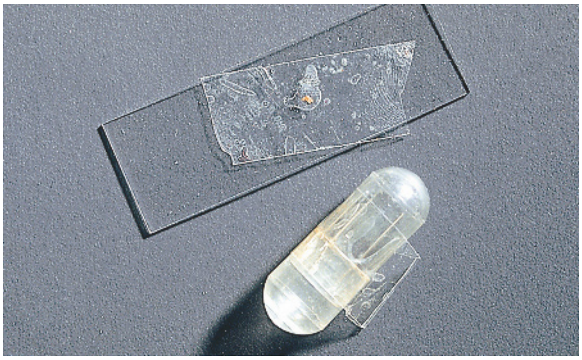


Fig. 20.5 Specimen brought in by a patient with delusions of parasitosis. From [54] with permission

20.6.4.3 Differential Diagnosis

Though the patient with delusions of parasitosis presenting to the dermatologist more frequently suffers from monosymptomatic hypochondriacal psychosis, it must be remembered that the presence of a delusional ideation may be one particular manifestation of a more global psychiatric derangement, such as schizophrenia or major depression.

Another subset of patients to consider are those patients who are substance abusers: drugs such as *cocaine* and amphetamine can induce formication and sometimes a delusional state that can be clinically identical to that of idiopathic delusions of parasitosis. Because the induction of formication is so well known among cocaine users, this phenomenon has been labeled cocaine *bugs* among the substance abusers.

Also, neurologic disorders such as multiple sclerosis [39] and pernicious anemia [41], and especially in the elderly brain dysfunction with manifest encephalomalacia due to cerebral arteriosclerosis [33], should be considered in the differential diagnosis.

Chronic tactile hallucinosis describes those unusual cases in which patients develop chronic tactile sensations without delusions or other definable psychiatric disturbances and without associated medical or neurologic conditions.

Finally, the presence of inflammatory and pruritic skin disorders or real infestation, such as pediculosis capitis and furunculoid myiasis of the scalp, should not be overlooked.

20.6.4.4 Treatment

Since trying to talk a patient out of a delusion is generally counterproductive, the most feasible way to have an impact on delusional ideation is to start the patient on an antipsychotic drug [19, 42]. Traditionally, pimozide is prescribed [8]; newer agents include risperidone and olanzapine. The most challenging aspect of managing patients with delusions of parasitosis is to try to get their cooperation in taking one of these agents. This results from the discrepancy between the patient's belief system and the clinician's understanding of the situation. The first step is to establish a good rapport with the patient. In trying to do so, it is important to recognize that the patient with delusions of parasitosis is expecting the clinician to treat him or her with respect as a skin patient, not as a psychiatric case. Therefore, the most effective approach is to take the chief complaint seriously, give the patient a good skin examination, and pay attention to whatever "specimens" are brought in. However, one should not make any comment that may reinforce the patient's delusional ideation. Once the clinician senses that a reasonable working relationship is established with the patient, psychopharmacological treatment is offered as an "empirical therapeutic trial," purposely avoiding any argument about the pathogenesis of the condition or the mechanism of action of the medication. No matter how skilful the clinician is, some delusional patients remain beyond reach. In this situation, the best the physician can do for the patient is simply to take on a supportive role and watch out for any secondary complication such as cellulitis, which may result from skin injury.

20.6.4.5 Prognosis

Untreated, the condition runs a chronic course. Many patients respond to pimozide, with symptomatic improvement occurring as early as 2 weeks after starting treatment, although several months of treatment may be needed for complete control. Most patients require ongoing maintenance therapy; some achieve remission; in a few, cure does occur. Remission is seldom associated with insight.

20.6.5 Scalp Dysesthesia

Scalp dysesthesia refers to patients who have only a disturbance in skin sensations of the scalp such as burning, stinging, or itching without apparent primary skin lesions and with a negative medical workup.

20.6.5.1 Pathogenesis

Scalp dysesthesia represents the manifestation of the cutaneous sensory disorders on the scalp [29]. If the sensations of cutaneous sensory disorders are felt in certain parts of the body, a specific term with the ending "dynia" is available to describe the condition, e.g., "glossodynia" for the painful tongue syndrome or "vulvodynia" for the vulvar pain syndromes. The term "trichodynia" does not appear to be specific, since in its original description it affected more than one-third of female patients complaining of hair loss. More recent findings demonstrating localization of neuropeptide substance P in the scalp skin of affected patients suggest a causal role of this neuropeptide, which is known to be involved in vascular tonus, neurogenic inflammation, and nociception. The role of substance P and other neuropeptides in the pathogenesis of trichodynia, and the relation of such substances to the psyche and emotional stress need further elucidation. For the time being, it is important to realize that a clinical diagnosis of trichodynia or scalp dysesthesia is not the final diagnosis, but only a starting point in reaching a conclusive interpretation of the symptoms [23]. Many of these patients may be classified as suffering from generalized anxiety disorder (DSM-IV 300.02, ICD-10 F41.1), depressive disorder (DSM-IV 300.4, ICD-10 F34.1) [27], conversion disorder (DSM-IV 300.11, ICD-10 F44.xx), or somatoform pain disorder (DSM-IV 307.xx, ICD-10 F45.4). Continued research into the chronic pain syndromes suggests that some may represent a neurologic dysfunction that in some cases is associated with a secondary psychiatric component.

20.6.5.2 Clinical Features

Women between the ages of 35 and 70 years are predominantly affected. They present with chronic unremitting pain and/or pruritus of the scalp, often coupled with the complaint that the hair is coming out in handfuls (see also: psychogenic pseudoeffluvium). The duration of symptoms may range from months to years. In some patients, symptoms are triggered or exacerbated by psychological or physical stress. In approaching patients with scalp dysesthesia, cases can be divided between those with positive findings in terms of psychiat-

ric symptoms, such as anxiety and depression [27], and those with no diagnosable psychiatric findings.

20.6.5.3 Differential Diagnosis

When confronted with a patient complaining of localized pain, one must consider possible underlying localized somatic disease, systemic organ disease, or psychiatric disease. Temporal arteritis, tension headache, and migraine equivalent are underlying medical conditions with symptoms that may include scalp pain.

20.6.5.4 Treatment

If there is an associated symptomatology of anxiety or depression, it is worth treating it, regardless of whether there is a causal relationship between the psychiatric findings and the cutaneous sensations, because it possible that patients who are anxious or depressed perceive discomfort of all types in an exaggerated manner. For patients who have no notable mental status findings, certain psychotropic medications can be used for their non-specific analgesic and antipruritic effects. The class of medications with the most well documented analgesic effect is the group of older tricyclic antidepressants, such as doxepin and amitriptyline. If pruritus is the primary problem, doxepin is the preferred agent; if pain is the primary sensation, amitriptyline would be preferred. If the patient cannot tolerate these agents, one may proceed next to the newer antidepressants such as imipramine or desipramine, or to the non-tricyclic agents, including fluoxetine. If the clinician suspects that the sensations the patient describes are hallucinatory in origin (*chronic tactile hallucinosis*), a therapeutic trial with pimozide is justified. Finally, gabapentin, an anticonvulsant medication, has been found to be effective in treating chronic pain syndromes (postherpetic neuralgia, erythromelalgia, and reflex sympathetic dystrophy) in uncontrolled studies. In the future this drug, and maybe a new generation of specific substance P antagonists, which are under development for the treatment of depression, may prove to be useful for managing scalp dysesthesia.

From a dermatologic point of view, care should be given to avoid overtreatment with various scalp applications. A patch test may be carried out to try to identify any offending agent that is producing itching or burning of the scalp. Typically, the various therapies prescribed to alleviate scalp discomfort are reported by the patient to make the condition worse. Patients may even develop an adverse reaction to placebo, the so-called nocebo response. Basically, dermatologic therapy should be restricted to the prescription of a non-irritating shampoo.

20.6.5.5 Prognosis

The prognosis depends on the underlying psychopathology and its appropriate treatment. A common denominator of many chronic pain syndromes is improvement or complete resolution with treatment with psychotropic agents. A strong psychiatric input from an experienced psychiatrist within a liaison clinic with the dermatologist is important, particularly in recognizing patients with significant depression or somatoform disorder who may be at suicide risk.

20.6.6 Psychogenic Pseudoeffluvium

Patients with psychogenic pseudoeffluvium are frightened of the possibility of going bald, or are convinced they are going bald without any objective findings of hair loss. Basically they suffer of what Cotterill has termed *dermatologic non-disease* [6]. Although dermatologists are used to seeing patients with minor skin and hair problems in significant body areas that cause disproportionate anxiety and cosmetic distress, with dermatologic non-disease there is no dermatologic pathology.

20.6.6.1 Pathogenesis

Once again, patients with psychogenic pseudoeffluvium have various mental disorders. The most common underlying psychiatric problems present are depressive disorder (DSM-IV 300.4, ICD-10 F34.1) and body dysmorphic disorder (DSM-IV 300.7, ICD-10 F45.2). The clinical spectrum is wide, and the majority of patients are at the neurotic end of the spectrum and merely have overvalued ideas about their hair, whereas a minority of patients are truly deluded and suffer from delusional disorder (DSM-IV 297.1, ICD-10 F22.0). These patients lie at the psychotic end of the psychiatric spectrum. Those parts of the body that are important in body image are the focus of the preoccupation and concern. Female patients are more likely to be preoccupied with the condition of their hair.

20.6.6.2 Clinical Features

A careful medical history, including medications, hormones, and crash diets, clinical examination of the hair and scalp (no alopecia, normal scalp), hair calendar (normal counts of hairs shed), trichogram (normal anagen and telogen rates), and laboratory work up (C-reactive protein, ferritin, basal thyroid-stimulating hormone, prolactin, estradiol, testosterone, and dehydroepiandrosterone sulfate or DHEAS) should be per-

formed to exclude real effluvium, and if necessary repeated [53].

It is important to question women who complain of excessive hair loss while no evidence of alopecia is evident on examination about depression and marital difficulties. Although female patients outnumber male patients, occasionally men are seen who blame their anxieties about their hair on their inability to socialize and meet with the opposite sex. In addition to the relentless complaint of hair loss, patients suffering from body dysmorphic disorder adopt obsessional, repetitive ritualistic behavior, and may come to spend the majority of the day in front of a mirror, repeatedly checking their hair. Another aspect of this behavior is a constant need for reassurance about the hair, not only from the immediate family but also from the medical profession and from dermatologists in particular. These patients may become the most demanding types of patient to try to manage.

20.6.6.3 Differential Diagnosis

True telogen effluvium resulting from androgenetic alopecia or female pattern hair loss, from chronic telogen effluvium or diffuse cyclic hair loss in women, and from involutional alopecia must be excluded. Differential diagnosis is complicated, since often there is considerable overlap between hair loss and psychological problems. Patients with hair loss have lower self-confidence, higher depression scores, greater introversion, as well as higher neuroticism and feelings of being unattractive.

20.6.6.4 Treatment

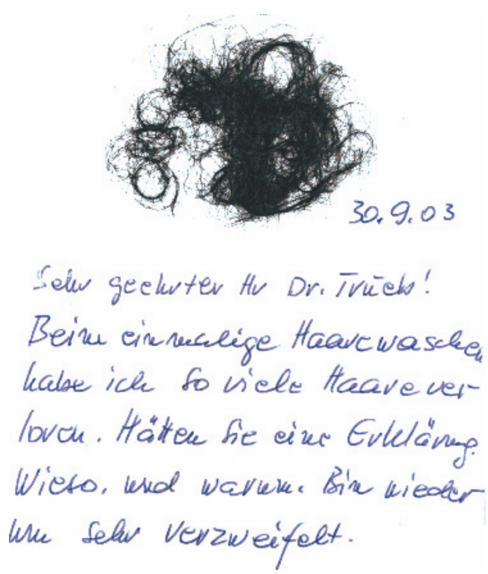
Once again, the first step is to establish a good rapport with the patient. In trying to do so, it is important to recognize that patients with psychogenic pseudoeffluvium are expecting the clinician to treat them with respect as a trichologic patient, and not as a psychiatric case. Therefore, the most effective approach is to take the chief complaint seriously and give the patient a complete trichologic examination. Patients with overvalued ideas may respond to a sympathetic and unpatronizing dermatologist.

Psychotherapy is aimed at any associated symptomatology of depression, regardless of whether there is a causal relationship between the psychiatric findings and the imagined hair loss, because it possible that patients who are depressed perceive even normal hair shedding in an exaggerated manner.

Patients with anxiety related to the fear of hair loss may also benefit from anxiolytic therapy with alprazolam or buspirone.

Many different treatments have been advocated to treat patients with body dysmorphic disorder [7]: a wide variety of psychotropic agents (including tricyclic antidepressants and benzodiazepines) and antipsychotic drugs (including pimozide and thioridazine) have been tried in this condition, with poor results. Although there have been no controlled clinical trials of treatment of patients with body dysmorphic disorder, preliminary data indicate that SSRIs, such as fluoxetine and fluvoxamine maleate, may be effective, though the effective dosage of the SSRI drugs needs to be higher than the dosage conventionally employed to treat depression, and the duration of treatment is long term. Response to this group of drugs takes up to 3 months, and not all patients with body dysmorphic disorder will respond to treatment with SSRIs. In patients who fail to respond to SSRIs given for 3 months, it has been suggested to add either buspirone to the SSRIs, or if the patient has delusional body dysmorphic disorder, to add an antipsychotic agent such as pimozide.

Patients with body dysmorphic disorder expect the solutions to their problems in dermatologic (trichotropic agents) or surgical terms (hair transplantation). Accordingly, following an initial consultation, it is common for a patient with body dysmorphic disorder to be given dermatologic treatment, either various scalp applications or antiandrogen therapy for alopecia. After repeated consultations with the patient, the dermatologist realizes that he or she is dealing with dermatologic non-disease. The result is often a frustrated dermatologist and a patient who eventually defaults from follow-up. The long


30.9.03

Sehr geehrter Hr Dr. Trüeb!
Beim einmalige Haarwasche
habe ich so viele Haare ver-
loren. Hätten Sie eine Erklärung
Wieso, und warum. Bin wieder
um sehr verzweifelt.

Fig. 20.6 Letter from a patient with psychogenic pseudoeffluvium sending a bundle of hair to Dr. Trüeb lost at each hair washing, desperately seeking advice

and tough consultations, repeated telephone calls, and constant need for reassurance can put a significant strain on the dermatologist involved. Finally, a minority of patients with dysmorphic body disorder are angry, and these patients can direct this anger not only at themselves but also at the attending physician, with reproachful letters (Fig. 20.6), threats, and even physical violence. It is important not to reject these patients and treat them mechanistically, but to adopt an empathetic approach.

20.6.6.5 Prognosis

The prognosis depends on the underlying psychopathology, its appropriate treatment, and the attending physician's capability to reassure and guide the patient.

Summary for the Clinician

Many patients with a hair or scalp disorder have psychological issues associated with their chief complaint. Most psychocutaneous conditions can be grouped as follows:

- *Psychophysiologic disorders*, in which the scalp disorder is exacerbated by emotional factors, e.g., seborrheic scalp dermatitis.
- *Primary psychiatric disorders* in which there is no real skin condition, but everything seen is self-induced, e.g., trichotillomania, neurotic excoriations, factitial dermatitis.
- *Cutaneous sensory disorders*, in which the patient has various abnormal sensations of the skin with no primary dermatologic lesions and no diagnosable somatic condition responsible for the sensations, e.g., scalp dysesthesia.
- And finally *secondary psychiatric disorders*, in which patients develop emotional problems as a result of hair loss, usually as a consequence of disfigurement due to alopecia.

Patients with psychocutaneous disorders are often reluctant to be referred to a psychiatrist, and the dermatologist is then the physician designated by the patient to handle the chief complaint. To handle these cases effectively, the dermatologist must be capable of classifying and diagnosing psychocutaneous disorders and of selecting the appropriate class of psychopharmacologic agent as indicated. Moreover, the best way to alleviate the emotional distress caused by a hair disorder is to effectively treat it: the intensity of the distress that the patient expresses should influence the clinician's decision to treat the hair disorder.

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Chapter 21

Photoepilation

Christine C. Dierickx

21

Synonyms

laser hair removal, hair removal by light, light-based hair removal, laser-mediated hair removal, laser epilation, light-assisted hair removal, photo-epilation, laser-assisted hair removal, intense pulsed light-based hair removal, selective photothermolysis of hair, selective electro-photothermolysis of hair, photodynamic therapy for hair removal, laser depilation, laser hair reduction, light-heat based photo-epilation, photo-assisted epilation, hair removal by laser and non-laser light systems, pulsed light source hair removal, optical hair removal, long-term laser hair removal, permanent laser hair removal

Key Features

- Light can destroy hair follicles by photothermal (local heating), mechanical (shockwaves, violent cavitation), and photochemical (generation of toxic mediators) means.
- Different light-based photo-epilation devices are available today (ruby laser, alexandrite, diode laser, Nd:YAG laser, intense pulsed light) based on the use of endogenous chromophores.
- New options include adding exogenous chromophores such as aminolaevulinic acid, carbon suspension, etc.
- Treatment technique, patient selection, actual technique and post-operative considerations have to be carefully planned.
- Expected benefits of photo-epilation must be kept realistic.
- Patients have to be well informed on possible side-effects and management of complications.

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21.1 Introduction

There has always been a need for an ideal method of hair removal that is both practical and effective. Traditional hair removal techniques included shaving, waxing, tweezing, chemical depilation, and electrolysis. Laser hair removal created controversy when it was first described about 10 years ago. Subsequently, it has become an accepted modality for long-term hair reduction. It rivals electrolysis in the successful treatment of small hair-bearing areas. It surpasses any modality in the treatment of larger hair-bearing anatomic areas.

21.2 History

The first laser-assisted hair removal device was marketed in 1996 [13]. Today such hair removal devices include ruby, alexandrite, diode and neodymium:yttrium aluminum garnet (Nd:YAG) lasers, intense pulsed light sources and combined radiofrequency (RF) and light sources. With the numerous lasers and non-laser light sources available today, one is faced with the question of which hair removal device to use. This article explains the mechanisms of using light to remove hair, examines the attributes of specific light device systems, and focuses on the treatment protocol for the various systems in order to provide a safe and effective treatment.

21.3 Technology

21.3.1 Mechanisms of Hair Follicle Destruction

There are three means by which light can destroy hair follicles: thermal (due to local heating), mechanical (due to shockwaves or violent cavitation) and photochemical (due to generation of toxic mediators such as singlet oxygen or free radicals). Removal of hair has been attempted by all three means (Table 21.1).

21.3.2 Photothermal Destruction

Photothermal destruction is based on the principle of selective photothermolysis [2]. The principle states that by choosing appropriate wavelength, pulse duration, and fluence, thermal injury can be confined to a target chromophore. In the visible to near-infrared region, melanin is the natural chromophore for targeting hair follicles. It is found in the hair shaft, the outer root sheath of the infundibulum, and the matrix area. Lasers or light sources that operate in the red or near-infrared wavelength region (694 nm ruby laser, 755 nm alexandrite laser, 800 nm diode laser, 1064 nm Nd:YAG laser and non-coherent light sources with cut-off filters) all lie in an optical window of the electromagnetic spectrum where selective absorption by melanin is combined with deep penetration into

Table 21.1 Methods for hair removal

I. Photothermal destruction	Normal mode ruby lasers (694 nm)
	Normal mode alexandrite lasers (755 nm)
	Pulsed diode laser (800 nm)
	Long-pulsed Nd:YAG lasers (1064 nm)
	Intense pulsed light source (590–1200 nm)
	Intense pulsed light sources and bipolar radiofrequency (590–1200 nm)
II. Photomechanical destruction	Carbon suspension – Q-switched Nd:YAG laser
	Q-switched Nd:YAG lasers
III. Photochemical destruction	Photodynamic therapy

the dermis. Deep, selective heating of the hair shaft, hair follicle epithelium, and the heavily pigmented matrix is therefore possible in the region of 600–1100 nm.

However, melanin in the epidermis presents a competing site for absorption. Selective cooling of the epidermis has been shown to minimize epidermal injury. Cooling can be achieved by various means including ice, a cooled gel layer, a cooled glass chamber, cooled sapphire window, a pulsed cryogen spray or cold air flow.

Laser pulse width also appears to play an important role, as suggested by thermal transfer theory. Thermal conduction from the melanin-rich shaft and matrix will heat surrounding follicular structures. To obtain spatial confinement of thermal damage, the pulse duration should be shorter than or equal to the thermal relaxation time of the hair follicle. Thermal relaxation of human terminal hair follicles has never been measured, but is estimated to be about 10–100 ms, depending on size. Therefore, devices for hair removal have pulse durations in the millisecond domain region. The normal-mode 694-nm ruby, normal-mode 755-nm alexandrite, 800-nm pulsed diode, and long-pulsed Nd:YAG lasers as well as filtered flash lamp technology all have pulse durations in the millisecond range.

However, sometimes the actual target is not pigmented and is at some distance from a pigmented structure. For example, the follicular stem cells, which line the outer root sheath in an area called the bulge near the attachment of the arrector pili muscle, are not pigmented and are at some distance from the pigmented hair shaft. These cells appear to be an important target for permanent hair destruction. The concept of thermal damage time (TDT) has therefore been proposed [1]. Pulses longer than the thermal relaxation time of the hair shaft allow propagation of the thermal-damage front through the entire volume to better damage the follicular stem cells. Super-long pulse heating (>100 ms) appears to allow for long-term hair removal.

Finally, hair removal is also dependent upon fluence. Careful studies with computerized hair counts have demonstrated that greater hair loss is achieved at the higher fluences tested. However, a patient's skin color will determine the highest tolerated fluence.

21.3.3 Photomechanical Destruction

Photomechanical destruction of hair has been attempted with very short nanosecond pulses by Q-switched 1064-nm Nd:YAG lasers, with or without carbon suspension [11]. However, when these very short pulses are used to target hair follicles, there is extremely rapid heating of the chromophore (melanin). This generates photoacoustic shock waves that cause focal photomechanical disruption of the melanocytes but no complete follicular disruption, leading in animals to leukotrichia but not to hair loss. Consistent with this behavior, temporary hair loss with an absence of permanent hair loss has been reported in humans, despite a decade of using Q-switched lasers widely for tattoo removal.

21.3.4 Photochemical Destruction

Photodynamic therapy is the use of light and a photosensitizer to produce a targeted photochemical reaction and therapeutic effect. Hair removal with topical aminolaevulinic acid (ALA) has been reported in a pilot study [12]. ALA is a precursor in porphyrin synthesis and is rapidly and selectively converted to protoporphyrin IX (PPIX) by cells derived from the epidermis and follicular epithelium. Upon absorption of a photon, PPIX efficiently crosses into an excited triplet state, which in turn generates singlet oxygen by collision with ground-state oxygen. Singlet oxygen is a potent oxidizer that damages cell membranes and protein. This is a so-called photodynamic reaction. A mean hair loss of 40% was reported in 12 volunteers after a single exposure to 630 nm light, 3 h after application of 20% ALA to the skin. A host of other porphyrins, chlorins, phthalocyanines, purpurins, and phenothiazine dyes can act as photodynamic agents and are under development as drugs for photodynamic therapy. It is likely that ALA or one of these other drugs will prove useful for hair removal.

21.4 Treatment Approach

The numerous lasers and non-laser light sources available today provide clinicians with multiple options. Several variables need to be considered when determining whether or not laser or light-assisted hair removal is appropriate for a particular patient and which technique to use. These include a patient's hair color, hair type, hair density, skin color, hormonal factors, and anatomical location. In order to determine the various critical factors for this procedure, the following general approach is used:

- A history is taken for appropriate patient selection.
- A physical examination is performed to evaluate skin color and skin condition, hair color, hair diameter and hair density.
- Instructions are given to the patient concerning pre-treatment hair management and skin care.
- Treatment guidelines are determined by skin and hair properties.
- Appropriate post-treatment care is provided.

21.4.1 Patient History

When obtaining a patient history, one wishes to obtain information that will enable the best result. It is vital to discuss patient expectations, medications, history of scarring, local infections, previous hair-removal strategies, endocrine status, recent sun exposure, and the patients' habits (i.e., sports, hot tub use, etc.). Patients with active cutaneous infections are not treated. Patients with a history of recurrent staphylococcal and herpes simplex infections are started on appropriate prophylaxis to diminish the likelihood of an outbreak. Although a history of keloids or hypertrophic scarring is not an absolute contraindication to treatment, individuals with these conditions are treated less aggressively. Although it has been reported that laser treatment of individuals who are taking isotretinoin is safe, the issue remains controversial. Patients on hormone therapy or with underlying endocrine abnormalities are alerted to the potential limitations of hair removal treatment. Caution should be exercised when treating patients who have known exposure to gold therapy. A case report indicated that a patient whose arthritis was treated with elemental gold was found to have green skin after treatment with a Q-switched Nd:YAG laser. It should also be noted that subsequent laser treatments eventually improved her cosmetic appearance. Patients with skin diseases such as vitiligo and psoriasis should be warned of the risk of koebnerization following laser surgery. Clinically this problem is rarely seen. In fact, anecdotal use of long-pulsed lasers to remove remaining pigmented skin in a patient with vitiligo was unsuccessful after multiple attempts. Q-switched lasers should also be avoided in hair-bearing areas that overly tattoos. A listing of previous hair-removal treatment modalities as well as response to this treatment modality should be recorded at the time of the initial consultation. Individuals with recent suntans should not be treated. At least 1 month of sun avoidance before the procedure has to be taken into account. Finally, patients should be carefully questioned on their onset of hair growth and evaluate for unknown medical problems (Table 21.2).

21.4.2 Physical Examination

When seeing a patient for the first time, the individual's skin type, hair color, and coarseness are noted, because this will determine which device is most ideal as well as predict response to treatment (Table 21.3). Location and density of excess hair should also be taken into consideration.

Table 21.2 History for laser/pulsed light hair removal

1. Presence of conditions that may cause hypertrichosis
a. Hormonal
b. Familial
c. Drug
d. Tumor
2. History of local or recurrent skin infection
3. History of herpes simplex, especially perioral
4. History of herpes genitalis, important when treating the pubic or bikini area
5. History of keloids/hypertrophic scarring
6. History of koebnerizing skin disorders such as vitiligo and psoriasis
7. Previous treatment modalities – method, frequency and date of last treatment, as well as response
8. Recent suntan or exposure to tanning or light cabinet
9. Present medications
a. Photosensitizing medications
b. Accutane intake within the past year

21.4.3 Preoperative Care

21.4.3.1 Six Weeks before Laser Treatment

Research has shown greater hair loss results at shaven rather than epilated sites, suggesting that light absorption by the pigmented hair shaft itself plays an important role. Patients, who seek optimal results, should therefore avoid plucking, waxing or electrolysis. Shaving and the use of depilatory creams will not interfere with laser hair removal results.

Use of a broad spectrum sunscreen is recommended. Sun avoidance must be practiced if hair removal is planned on sun-exposed sites. A bleaching cream such as 3% hydroquinone, retinoic acid 0.025% and hydrocortisone 2% can be prescribed to patients with darker skin types or who have received recent sun exposure.

21.4.3.2 Day before Laser Treatment.

The patient is instructed to shave the area to be treated. If the patient is uncomfortable with the idea of shaving the area, a depilatory cream can be used instead. Alternatively shaving may be done on the day of treatment after physician assessment is performed. Use of prophylactic antiviral agents such as valacyclovir, famciclovir or aciclovir may be started, when indicated on the day of the procedure.

21.4.3.3 Day of Treatment

The area to be treated should be clean and free of make-up. If needed, 1–2 h before the scheduled laser treatment, a thick layer of a topical anesthetic cream [e.g., Emla (Astra-Zeneca, Wilmington, DE), ELA-Max (Ferndale Laboratories, Ferndale, Mich.) or Topicaine (ESBA Laboratories, Mountain View, Calif.)] may be applied with a cover of plastic wrap. If shaving is done on the day of treatment, it should precede application of topical anesthetic.

21.4.4 Laser and Light Source Selection

21.4.4.1 Endogenous Chromophore

21.4.4.1.1 694-nm Ruby Lasers

Of the original five normal-mode, 694-nm ruby lasers, only two are still commercially available for hair removal (Table 21.4). These include the RubyStar and Sinon. Because of high melanin absorption at 694 nm, the ruby lasers are best indicated in light-skinned (Fitzpatricks's skin type I–III) individuals with dark hairs.

The E2000 (Palomar) uses a sapphire-cooled hand piece (Epiwand™) to protect the epidermis. The sapphire lens is actively cooled to 0 or −10°C and put in direct contact with the skin. Compared to air as an external medium, the sapphire provides heat conduction away from the epidermis before, during, and after each laser pulse. It permits beam coupling with the skin and internal reflection reduction by index matching. In addition to surface cooling, the Epiwand™ sapphire hand piece has other distinct advantages. The sapphire lens provides a convergent beam to maximize delivery of light into the dermis. Its surface allows for application of pressure on the skin surface, which deforms the dermis and decreases the distance from the epidermis to the deeper follicular structures. In addition, the pressure blanches the underlying blood vessels, minimizing absorption of laser energy by hemoglobin. Light is delivered through a fiber and two different spot sizes are available (10 and 20 mm). A retro-reflector is build into the hand piece, which allows for photon recycling and therefore suffi-

Table 21.3 Indications and expected efficacy for different hair-removal devices

Laser or Light Source	Skin type	Hair color	Hair diameter	Expected efficacy
Normal-mode Ruby	I–III	Dark to light brown	Fine and coarse	Long-term hair removal
Normal-mode Alexandrite	I–IV	Dark to light brown	Fine and coarse	Long-term hair removal
Pulsed diode	I–V	Dark to light brown	Coarse	Long-term hair removal
Normal-mode Nd:YAG	I–VI	Dark	Coarse	Long-term hair removal
Q-switched Nd:YAG	I–VI	Dark to light brown	Fine and coarse	Temporary hair removal
Intense pulsed light	I–VI	Dark to light brown	Coarse	Long-term hair removal

Table 21.4 Hair removal using laser

Light source	Wavelength (nm)	System name	Pulse duration	Fluence (J/cm²)	Spot size (mm)	Repetition rate (Hz)	Other features
Long pulse ruby	694	E2000 * (Palomar)	3–100 ms	10–40	10, 20	1	Cooling handpiece 0–10ºC Fiber delivery; photon recycling
		EpiPulse Ruby * (Lumenis)	1.2 ms	10–40	3–6	1.2	Triple pulse technology
		Chromos * (Mehl Biophile)	800 µs	10–25	7	0.4–0.6	
		Ruby Star (Aesclepion-Meditec)	4 ms	Up to 24	Up to 14	1	Dual mode: may also be Q-switched
		Sinon (Wavelight)	4 ms	Up to 30	5, 7, 9	0.5–2	Cold air unit May also be Q-switched
Long pulse alexandrite	755	Apogee (Cynosure)	0.5–300 ms	25–50	5, 10, 12, 15	3	Cold air or integrated cooling
		Gentlelase (Candela)	3 ms	10–100	6, 8, 10, 12, 15, 18	Up to 1.5	Dynamic cooling device
		Epitouch ALEX (Sharplan) *	2–40 ms	Up to 50	5, 7, 10	1	Scanner option
		Ultrawave II/III (Adept Medical)	5–50 ms	5–55	8, 10, 12	1–2	Available with 532 nm and/or 1064 nm Nd:YAG
		Epicare (Light Age)	3–300 ms	25–40	7, 9, 12, 15	1–3	
		Arion (WaveLight)	1–50 ms	Up to 40	6, 8, 10, 12, 14	Up to 5	Cold air unit

Diode laser	800	LightSheer (Lumenis)	5–400 ms	10–100	9×9, 12×12	Up to 2	Cooling handpiece
		Apex-800 (Iridex)	5–100 ms	5–60 (600 W)	7, 9, 11	Up to 4	Cooling handpiece
		SLP1000™ (Palomar)	5–1000 ms	Up to 575	12	Up to 3	SheerCool™ triple contact cooling, photon recycling
		MedioStar (Aesclepion-Meditec)	50 ms	Up to 64	10, 12, 14	Up to 4	Integrated scanner with cold air cooling device
		F1 Diode Laser (Opusmed)	15–40 ms	10–40	5, 7	4	
		EpiStar (Nidek)	5–700 ms	0.12–400	2, 3, 4, 5	1–15	
Q-Switched Nd:YAG	532/1064	Softlight (Telsar)	12–18 ns	2.5–3	7	Up to 10	Only 1064 nm
		MedLite C6 (Hoya/ConBio)	<20 ns	Up to 12	3, 4, 6, 8	Up to 10	532 and 1064 nm

Table 21.4 (*continued*) Hair removal using laser

Light source	Wavelength (nm)	System name	Pulse duration	Fluence (J/cm^2)	Spot size (mm)	Repetition rate (Hz)	Other features
Long-pulsed Nd:YAG	1064	CoolGlide (Cutera)	0.1–300 ms	up to 300	3, 5, 7, 10	Up to 2	Contact pre-cooling
		Lyra/Gemini (Laserscope)	20–100 ms	5–900	10		Contact cooling Photon recycling
		Ultrawave (Adept Medical)	5–100 ms	5–500	2, 4, 6, 8, 10, 12	1–2	Available with 532 nm and/or 755 nm
		Athos (Quantel)	3.5 ms	Up to 80	4	Up to 3	
		Gentle Yag (Candela)	0.25–300 ms	Up to 600	1.5, 3, 6, 8, 10, 12, 15, 18	Up to 10	Cryogen spray optional
		Varia (CoolTouch)	300–500 ms	Up to 500	3–10		Pulsed cryogen cooling with Thermal Quenching
		Acclaim 7000 (Cynosure)	0.4–300 ms	300	3, 5, 7, 10, 12	5	Cold air or integrated cooling
		Smartepil II (Cynosure)	Up to 100 ms	16–200	2.5, 4, 5, 7, 10	6	Smart cool scanner
		Dualis (Fotona)	5–200 ms	Up to 600	2–10		
		Vasculight Elite (Lumenis)	2–16 ms	70–150 J	6	0.33	Combined with IPL
		Profile (Sciton)	0.1–200 ms	Up to 400			Combined with erbium
		Mydon (WaveLight)	5–90 ms	10–450	1.5, 3, 5, 7, 10	1–10	Contact or air cooling

Intense pulsed broadband light source	590-1200	EpiLight (Lumenis)	15–100 ms	Up to 45	10×45, 8×35	0.5	Contact cooling; multiple pulsing
	695-1200	Quantum HR (Lumenis)	15–100 ms	25–45	34×8 mm	0.5	
	400- 950	Ellipse (DDD)	0.2–50 ms	Up to 21	10×48	0.25	Dual mode filtering technique
	400-1200	PhotoLight (Cynosure)	5–50 ms	Up to 16	46×18		Xenon pulsed lamp
	500-1200	Estelux (Palomar)	10–100 ms	4–40	16×46	Up to 1	Fast coverage rate Coolroller™ cooling
	550-900	ProLite (Alderm)		10–50	10×20, 20×25	0.5	FLP (fluorescent pulsed light)
	400-1200	Spatouch (Radiancy)	35 ms	Up to 7	22×55	0.25	Light heat energy (LHE)
	510-1200	Quadra Q4 (Derma Med USA)	48 ms	10–20	33×15		Quad pulsed light system
	510-1200	SpectraPulse (Primary Technology)	3×12 Pulse delay: 4 or 5	10–20	15×33		Light energy recycling (LER)
IPL+Nd:YAG	515 – 1200	VascuLight Elite (Lumenis)	0.5–25 ms	3–90	35×8		Contact cooling/ combined with 1064
	400-1200	StarLux (Palomar)	5–500 ms	Up to 30	16×46		
ELOS technology	Optical energy (580–980 nm) combined with electrical energy (radiofrequency)	Aurora DS (Syneron)		Light energy 10–30 RF energy 5–20 J/cm^3	12×25	0.7	Cooling (5–20°C on skin surface) combined with skin impedance control

cient energy delivery. Depending on skin type or hair thickness, a single pulse (3 ms) or twin pulse (100 ms, i.e., two 3-ms pulses, delivered with a delay of 100 ms) can be chosen [4].

The EpiPulse™ long-pulsed Ruby (Lumenis, Santa Clara, Calif.) employs a triple-pulse technology with a 10-ms interval between pulses. It keeps the follicle temperature at a sufficient level to cause destruction while the epidermis temperature remains below damage threshold. This synchronized pulsing technology should make treatment of darker skin types possible. Cooling of the epidermis is achieved by applying a thick layer of cooled transparent gel on the skin. A thin, patented, laser-aligning sheet can be placed on top of the cooling gel, which enables proper positioning of the laser beam and helps to ensure uniform laser application to all intended areas.

The RubyStar (Aesculap-Meditec, Jena, Germany) and the Sinon ruby laser (Wavelight, Erlangen, Germany) are dual-mode ruby lasers. They can operate in the conventional Q-switched mode for the treatment of tattoos and pigmented lesions, as well as in the normal mode for hair removal. An integrated cooling device consisting of a cooled contact hand piece (RubyStar) or cold air cooling (Sinon) cools the skin prior to laser pulse delivery.

Grossman et al. initially reported selective injury to hair follicles by a long pulse ruby laser [13]. Thirteen patients with fair skin and dark hair were treated once on the thighs or back at fluences of 20–60 J/cm² with a spot size of 6 mm. Hair growth delay was induced for 1–3 months in all subjects at all fluences. Biopsy samples obtained immediately after treatment showed selective thermal damage to pigmented hair follicles, with vaporization of the hair shafts, large patches of necrosis in the follicular epithelium, and occasional rupture with perifollicular dermal injury suggestive of steam vents. Transient pigmentary changes occurred in several patients but scarring was not observed. At 1–2 years' follow-up, four of seven recalled patients had persistent hair loss, which was greatest in sites treated at the highest fluence [7]. Biopsy samples from one patient showed a reduced number of terminal hairs with a reciprocal increase in small vellus-like hairs, but no evidence of fibrosis or destruction of hair follicles. It was suggested that permanent hair loss after 0.3-ms ruby laser treatment results from miniaturization of the follicular bulb and papilla, alike to the mechanism of androgenetic alopecia.

Additional studies with larger numbers of patients have confirmed that hair counts are reduced by approximately 30% after a single treatment with the ruby laser. The effects of multiple treatment sessions are additive, as hair counts are reduced by approximately 60% after three or four treatment sessions [6].

21.4.4.1.2 755-nm Alexandrite Lasers

Several long-pulsed alexandrite lasers (755 nm) are available for hair removal. At this longer wavelength, the ratio of energy deposited in the dermis to the epidermis is greater because of greater depth of penetration. The risk for epidermal damage in darker skin types is therefore reduced. Five different alexandrite lasers are available (Table 21.4). These include Apogee (Cynosure, Chelmsford, Mass.), Epitouch Alex (Lumenis, Santa Clara, Calif.), GentleLase (Candela, Wayland, Mass.), Ultrawave II-III (Adept Medical, Rancho Santa Margarita, Calif.) and Epicare (LightAge, Somerset, N.J.).

The Apogee laser provides pulse durations of between 0,5 and 300 ms and fluences up to 50 J/cm². A cooling hand piece (SmartCool™) allows a continuous flow of chilled air to the treatment area. Epitouch Alex has a high repetition rate (5 Hz), and a scanner that can cover an area of 40×40 mm² area within 6 s. GentleLase employs a dynamic cooling device (DCD) to protect the epidermis. This DCD cooling method uses short (5–100 ms) cryogen spurts, delivered to the skin surface through an electronically controlled solenoid valve; the quantity of cryogen delivered is proportional to the spurt duration. The liquid cryogen droplets strike the hot skin surface and undergo evaporation. Skin temperature is reduced as a result of supplying heat for vaporization. This cooling method allows for fast and selective cooling of the epidermis. The UltraWave II and III offers the convenient combination of 755 and 1064 nm wavelength in a single device and is well suited for removing unwanted hair in all skin types. Epicare laser has a cold air cooling option and a Smartscreen software package that assists in record keeping, protocols, and even practice management.

McDaniel et al. [18] showed after one treatment with the variable-pulse alexandrite laser on the lip, leg, and back a 40%–56% reduction of hair growth at 6 months, and Touma and Rohrer demonstrated a 70% decrease in hair counts at 60 months after a single treatment on the forearm with a 3-ms alexandrite laser [24]. Goldberg and Ahkami [10] compared both the 2-ms and 10-ms pulse durations on 14 subjects who ranged in phototypes from I to III. At 6 months, hair counts did not show a statistically significant difference between the two pulse widths. Nanni and Alster [19] showed in 36 subjects at 6 months equivalent long-term hair removal with the long-pulsed alexandrite at pulse durations of 5, 10, and 20 ms. Post inflammatory hyperpigmentation occurred in 3% of patients. It was generally less severe and resolved quicker in the test spots treated with the 20-ms-long pulses in comparison to the 5- and 10-ms pulse widths. From these studies, it is uncertain whether pulse durations of 2, 5, 10 and 20 ms show a significant clinical difference in terms

of efficacy. However, the longer pulse durations provided better protection to the epidermis.

21.4.4.1.3 800-nm Diode Lasers

An extremely high-powered (2900 W) diode laser (LightSheer, Lumenis, Santa Clara, Calif.) is a popular laser hair-removal device. Long-term results suggest that the pulsed, 800-nm diode laser is very effective for removal of dark, terminal hair: permanent hair reduction can be obtained in 89% of patients [5]. This laser operates at 800 nm, has pulse widths between 5 and 400 ms, a 12×12 mm spot, a 2-Hz repetition rate, fluences between 10 and 60 J/cm², and a patented contact cooling device (ChillTip™). Because of the longer wavelength, the active cooling and the longer pulse widths, darker skin types can be treated more safely.

Several other 800-nm diode lasers (Apex-800, Iridex, Mountain View, Calif.; F1 diode laser, Opus Medical, Montreal, Canada; Mediostar, Asclepion-Meditec, Jena, Germany; SLP1000, Palomar, Burlington, Mass.; and EpiStar, Nidek, Gamagori, Japan) are available (Table 21.4).

21.4.4.1.4 Q-Switched 1064-nm Nd:YAG Laser

A high-powered, 1064-nm Q-switched Nd:YAG laser (MedLite IV, Conbio, Santa Clara, Calif.) is available for hair removal. This laser has a very short pulse duration in the nanosecond range, a 4-mm spot, a repetition rate of 10 Hz and fluences up to 8–10 J/cm². The high repetition rate (10 Hz) delivers the laser pulses very rapidly and therefore large areas can easily be covered and operative time is significantly shortened. The longer wavelength (1064 nm) makes it useful for darker skin types. Although capable of inducing a growth delay it appears to be ineffective for long-term hair removal.

21.4.4.1.5 Long-Pulsed 1064-nm Nd:YAG Lasers

Several long-pulsed Nd:YAG lasers (1064 nm wavelength), which deliver pulses in the millisecond domain, are now available for hair-removal laser treatment on all skin types (Table 21.4). These lasers include Lyra or Gemini (Laserscope, San Jose, Calif.), CoolGlide (Cutera, Brisbane, Calif.), Ultrawave (Adept Medical, Rancho Santa Margarita, Calif.), Profile (Sciton, Palo Alto, Calif.), VascuLight (Lumenis, Santa Clara, Calif.), SmartEpiII and Acclaim (Cynosure, Chelmsford, Mass.), Athos (Quantel, Les Ulis Cedex, France), Dualis (Fotona, Ljubljana, Slovenia), Varia (CoolTouch, Roseville, Calif.), Mydon (Wavelight, Erlangen, Germany), and GentleYAG (Candela, Wayland, Mass.).

The long-pulsed Nd:YAG lasers have a deeply penetrating wavelength of 1064 nm. The reduced melanin absorption at this wavelength necessitates high fluences in order to adequately damage hair. However, the poor melanin absorption at this wavelength coupled with epidermal cooling makes the long-pulsed Nd:YAG a potentially safe laser treatment for darker skin types up to VI [3]. The Nd:YAG laser is also often used for treatment of pseudofolliculitis barbae, a skin condition commonly seen in darker skin types [21].

21.4.4.1.6 Pulsed, Non-Coherent Broadband Light Sources

For several years now, intense pulsed, non-laser light sources, emitting non-coherent, multi-wavelength light have also been used for hair removal (EpiLight, Lumenis, Santa Clara, Calif.; Ellipse, Danish Dermatologic Development, Hørsholm, Denmark) (Table 21.4). By placing appropriate filters on the light source, wavelengths ranging from 590 to 1200 nm can be generated. Cut-off filters are used to eliminate short wavelengths so that only the longer, more deeply penetrating wavelengths are emitted. Pulse durations vary in the millisecond domain. A single or multiple pulse mode (two to five) with various pulse delay intervals can be chosen. The wide choice of wavelengths, pulse durations and delay intervals makes this device potentially effective for a wide range of skin types. The devices come with software which guides the operator in determining treatment parameters depending on the patient's skin type, hair color, and coarseness.

Some of the latest hair-removal technologies to emerge are the cheaper, small, pulsed light hair-removal systems. These include the IPL Quantum HR (Lumenis, Santa Clara, Calif.), the ProLite (Alderm, Irvine, Calif.), the SpaTouch photoepilation system (Radiancy, Orangeburg, N.Y.), PhotoLight (Cynosure, Chelmsford, Mass.), Quadra Q4 (DermaMed USA, Lenni, Pa.), SpectraPulse (Primary Technology, Tampa, Fla.), and the Estelux (Palomar , Burlington, Mass.). These systems have been optimized for hair removal with wavelengths preferentially absorbed by melanin, long pulse widths, and large spotsizes.

Recently, IPL systems have been developed that are combined with 1064 nm laser light (VascuLight, Lumenis, Santa Clara, Calif. and Starlux, Palomar, Burlington, Mass.). These devices should allow for treatment of a wide spectrum of hair and skin colors.

Several studies have demonstrated the long-term efficacy of IPL hair-removal devices: a mean reduction of

83% at 12 months or more after two to six treatments can be obtained [9].

21.4.4.1.7 Electro-Optical Synergy (ELOS™) Technology

ELOS™ technology utilizes a synergy between electrical (conducted RF) and optical (laser or light) energies. The electrical energy causes heat that is focused on the hair follicle and the bulge area, while the optical energy heats mainly the hairshaft. When combined, a uniform temperature distribution across the hairshaft and the follicle should be obtained to achieve effective hair removal. Based on this ELOS™ technology, Syneron (Yokneam Illit, Israel) has developed a system (Aurora) that combines RF energy with intense pulsed light and is equipped with cooling. The use of the RF energy should also allow for treatment of all skin types, since this form of energy is not absorbed by epidermal melanin [23].

21.4.4.2 Exogenous Chromophore

Rather than targeting endogenous melanin, an exogenous chromophore can be introduced into the hair follicle and then irradiated with light of a wavelength that matches its absorption peak. This eliminates the problem of competition by epidermal melanin. The main problem is finding a reliable method for the chromophore to penetrate to all depths of the hair follicle.

21.4.4.2.1 Carbon Suspension-Q-Switched Nd:YAG Laser

In this method, an exogenous chromophore (carbon suspension) with a peak absorption in the near-infrared portion of the spectrum is used in combination with a Q-switched Nd:YAG laser. The Softlight system (Telsar, Wood River, Ill.) uses a proprietary suspension of 10-μm-diameter carbon particles applied to wax-epilated skin. The skin, after being wiped clean of the topical carbon material, is irradiated with relatively low energies (2–3 J/cm²) of Q-switched Nd:YAG laser light (1064 nm, 10 Hz, 10-ns pulse duration, 7-mm spot size). However, the short pulse duration of the laser used in this technique limits the extent of follicular damage. This technique therefore can successfully induce a delay in hair growth, but fails to produce long-lasting hair removal. However, when compared to laser treatment alone, no added benefit is obtained with waxing or carbon suspension application [19].

21.4.4.2.2 Meladine™

Meladine™ is a topical melanin-encased phosphatidylcholine-based liposome solution which, when sprayed on the desired area, supposedly selectively deposits melanin directly into the hair follicle without staining surrounding skin. The proprietary liposome molecules are small enough to potentially penetrate the infundibulum. The result should be temporarily melanin-rich follicles, which allows patients with lighter hair colors to benefit from laser hair removal.

In European clinical studies, 90% of patients with light colored hairs pre-treated with Meladine™ experienced permanent hair reduction of 75% or more as compared with 0% of patients who did not receive Meladine™ treatment. The effectiveness of the treatment was directly proportional to the amount of Meladine™ used. In fact, those patients who used 86 ml or more in their pre-treatment regimen experienced hair reduction of 95% (J. De Leeuw, presented at the 2002 EADV meeting). Conversely, a study by Drs. Tanzi and Alster using Meladine™ found growth delay, but not permanent hair loss in subjects treated (presented at the 2003 American Society for Dermatologic Surgery meeting).

21.4.4.2.3 Aminolaevulinic Acid

Photodynamic therapy (PDT) involves the use of a photosensitizer and light to produce therapeutic effects. The mechanism of action is presumed to involve the generation of toxic reactive oxygen species, subsequent to the photochemical activation of the photosensitizer by light. The recent introduction of 5-aminolaevulinic acid (5-ALA), as a topical photosensitizer, has opened up a variety of potential therapeutic options. Selective protoporphyrin IX (PPIX) synthesis in pilosebaceous units is a unique feature of ALA over other photosensitizers and topical application circumvents the photosensitivity that is induced by systemic agents.

In a small pilot study of 12 subjects, 5-ALA was applied topically to hair-bearing skin after wax epilation. Test sites were irradiated 3 h later with 630 nm light from an argon-pumped tunable dye laser. At 6 months following a single treatment, a dose-dependent decrease in hair regrowth was observed, with the greatest loss (40%) occurring in areas that received the highest doses of light (200 J/cm²). Temporary hyperpigmentation was the only adverse effect noted.

Preliminary reports from a recent study including 30 patients examined the ability of a 20% topical solution of aminolaevulinic acid HCl (Levulan® stick, DUSA Pharmaceuticals, Wilmington, Mass.) with ei-

ther a proprietary non-laser light source or a laser to remove human hair. The non-laser light plus Levulan® did not result in more significant hair loss than placebo plus light. However, Levulan® plus laser light appears to prevent approximately 30% of the hair from regrowing with one treatment [unpublished results from DUSA Pharmaceuticals].

Photodynamic therapy may be a useful approach for hair removal. Since photosensitizers tend to localize in the follicular epithelium, photochemical destruction of all hair follicles, regardless of hair color or growth cycle, could potentially be obtained. Long-term data and large-scale studies are needed to determine the safety and long-term efficacy of this modality.

21.4.5 Treatment Technique

The procedure for hair removal is similar using any of the devices previously described. Anesthetic cream, make-up, and skin cream must be removed from the treatment site. Although less-sensitive areas (back, legs, arms) can frequently be treated without anesthesia, topical anesthesia is generally used on more sensitive areas. When treating the upper lip, local or regional anesthesia with lidocaine is sometimes required.

A treatment grid can be applied in order to provide the operator with an outline of the area to be treated. In the absence of a grid careful attention must be paid to prevent double treatment and skipped areas. Visibility can also be increased by the Syris™ Visualization system, a polarized headlamp with magnifying loupe (Syris Scientific, Gray, Mass.).

The ideal treatment parameters must be individualized for each patient. If needed, test sites can be placed at inconspicuous sites in the area to be treated. The treatment fluence is carefully increased while the skin is observed for signs of acute epidermal injury, such as whitening, blistering, ablation or Nikolsky's sign. Slightly overlapping laser pulses should be delivered with a pre-determined spot size. It is recommended that the largest spot size and the highest tolerable fluence be used to obtain the best results.

If the device is not equipped with a cooling device, a thick layer of cooled gel is applied before delivery of the laser pulses. With the Dynamic Cooling Device™ (Gentlelase, Candela), short bursts of cryogen spurts (5–80 ms) are delivered automatically onto the skin surface, immediately prior to delivery of the laser pulse. The Apogee laser (Cynosure) uses a cooling handpiece (SmartCool™) that allows a continuous flow of chilled air to the treatment area. The Coolglide uses a copper plate that pre-cools the area to be treated. The Epilaser, LightSheer and Lyra/Gemini use a sapphire cooled handpiece (Epiwand™, Chilltip™ and Versastat™ respectively) that is placed in direct contact with the skin. Prior to pulse delivery, the handpiece is pressed firmly against the skin. After delivery, the handpiece is picked up and placed firmly on an adjacent site, until the entire area is covered. The sapphire contact cooling tip should be wiped clean every five to ten pulses to remove debris. Between patients, disinfection of the handpiece is mandatory.

The ideal immediate response is vaporization of the hair shaft with no other apparent effect. After a few minutes, perifollicular edema and erythema may appear. The intensity and duration depend on the hair color and hair density. If there is a sign of epidermal damage, the fluence should be reduced.

21.4.6 Post-Operative Considerations

Ice packs reduce post-operative pain and minimize edema. Analgesics are not usually required unless extensive areas have been treated. Prophylactic courses of antibiotics or antivirals should be completed when indicated. Topical antibiotic ointment applied twice daily is indicated if any epidermal injury occurred. Mild topical steroid creams may be prescribed to reduce post-treatment edema and erythema. Any trauma (e.g., picking or scratching) to the treated area should be avoided. During the first week of healing, direct sun exposure should be avoided or sunblocks used. Make-up may be applied on the day following treatment unless blistering or crusts develop. The damaged hair is often shed during the first few weeks after treatment. Patients should be reassured that this is not a sign of hair regrowth.

21.5 Subsequent Treatments

Research has shown that laser hair removal requires the presence of a pigmented hair shaft. Retreatment can therefore be performed as soon as regrowth appears. Regrowth is based on the natural cycle, which varies by anatomic location, but on average, the timing is 6–8 weeks.

21.5.1 Expected Benefits

Generally, the average number of hair-removal treatments to achieve a significant reduction of excess hair is between five and seven treatments performed at 1- to 3-month intervals. Clinical improvement includes ab-



Fig. 21.1 **a** Patient with hirsutism due to polycystic ovary syndrome. **b** Significant reduction of hair growth at 9 months after fifth laser hair removal treatment

solute hair number reduction, finer, lighter regrowing hair, and slower regrowth.

The concept of hair removal has been defined in the following way. "Temporary hair loss" is defined as a delay in hair growth, which usually lasts for 1–3 months, consistent with the induction of telogen. "Permanent hair reduction" refers to a *significant* reduction in the number of *terminal* hairs after a given treatment, which is *stable* for a period of time longer than the complete growth cycle of hair follicles at the given body site. Recently, it has been suggested to add another 6 months to this post-treatment observation time, i.e., the time it takes for a damaged follicle to recover from the laser injury and reenter a normal growth cycle [20].

A distinction needs also to be made between permanent and complete hair loss. Complete hair loss refers to a lack of regrowing hairs (i.e., a significant reduction in the number of regrowing hairs to zero). Complete hair loss may be either temporary or permanent. Laser treatment usually produces complete but temporary hair loss for 1–3 months, followed by partial but permanent hair loss.

Patients have different expectations of treatment (e.g., temporary versus permanent, partial versus complete hair removal). All responses are clinically significant and may be separately desirable for different patients. Growth delay that provides a few months of hairless skin is far more reliably achieved than permanent hair loss. All laser systems have been shown to temporarily reduce hair growth for all hair colors (except white) and at all fluences. Except for one report [22], blonde, red or gray-haired patients are unlikely to experience a permanent reduction, but hair loss in these patients can be maintained by treatment at approximately 1- to 3-month intervals.

Effectiveness for permanent hair reduction is strongly correlated with hair color and fluence. Long-term controlled hair counts indicate an average of 20%–30% hair loss with each treatment, indicating the need for multiple treatments to obtain near-complete hair removal. Research also shows that in the ideal patient with fair skin and dark hair, the probability for long-term hair removal is about 80%–89%, depending on the device used. Long-term comparison of different lasers (ruby, alexandrite, diode, Nd:YAG) and light sources (intense pulsed light) indicates that effective long-term hair removal can be achieved with all systems (Figs. 21.1, 21.2, 21.3).

The maximum fluence tolerated is determined by the epidermal pigmentation. Fair-skinned, dark-haired patients are most easily treated. Dark-skinned patients pose a greater challenge. Any of the hair-removal devices are safe and effective in light-skinned patients while longer wavelengths (near-infrared) and longer pulse durations have been shown to treat darker skin types more safely when combined with cooling devices. A Q-switched Nd:YAG laser, with or without an external chromophore, has been shown to be very useful for treatment of dark skin types but appears to be ineffective for permanent hair removal. For patients presenting with recent sun exposure, pre-treatment with a bleaching agent, sunscreen, and/or sun avoidance is recommended prior to laser treatment.

The number of treatments needed to obtain the best results for different anatomical sites is unknown. Generally, the average number of hair-removal treatments



Fig. 21.2 **a** Patient consulting for laser hair removal of axillary hair. **b** Result at 6 years after fourth laser hair removal treatment

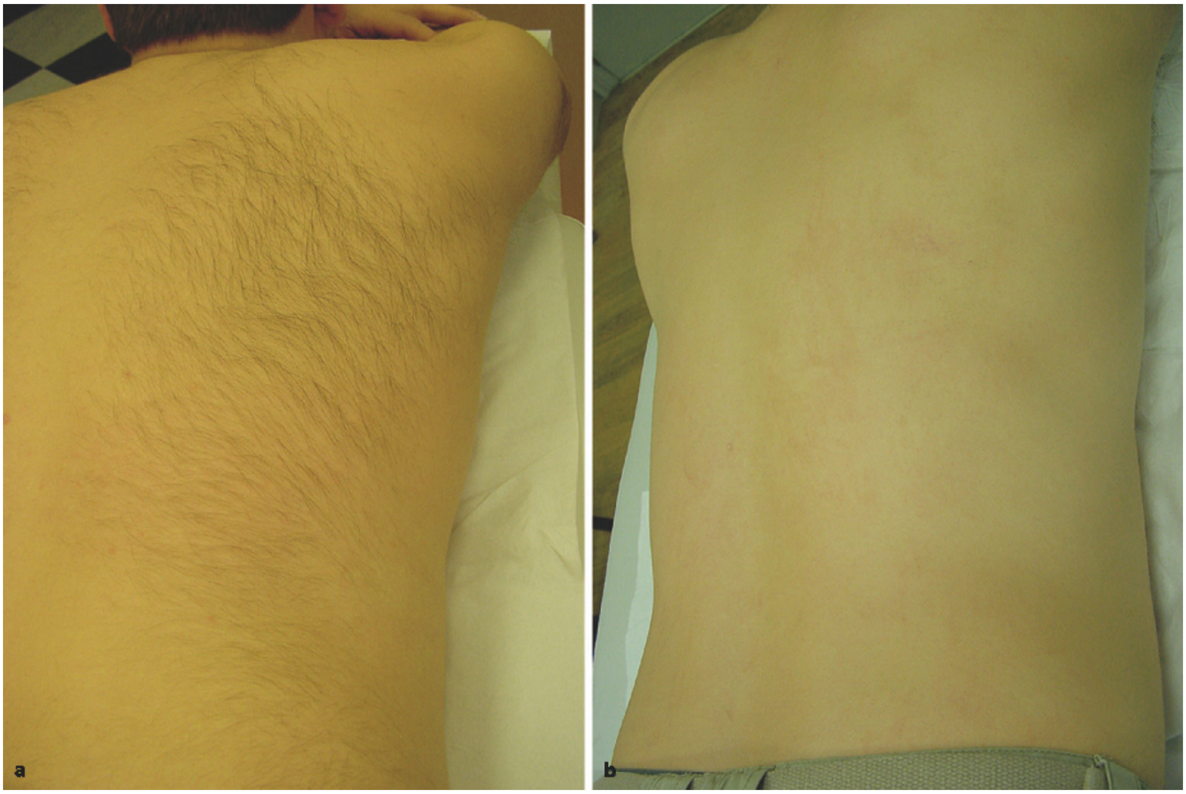


Fig. 21.3 **a** Patient with hairy back before IPL treatment. **b** Result at 6 months after seventh IPL hair-removal treatment

needed to achieve a significant reduction of excess hair is between five and seven performed at 1- to 3-month intervals. A rare patient can obtain long-term complete hair removal after a single treatment, while others may respond poorly, for as yet unknown reasons. However, most patients (80%–89%) respond favorably.

Often, regrowing hairs are thinner and lighter in color, as indicated by measurements of diameter and color of regrowing hairs. This also contributes to the overall cosmetic outcome since the clinical impression of hairiness is defined not only by the absolute number of hairs, but also by the color, the length, and the diameter of the hairs. The range of outcomes can be summarized as absolute hair number reduction, finer, lighter regrowing hair, and slower regrowth.

Animal studies have shown that the hair growth cycle affects hair follicle destruction achieved by ruby laser pulses: actively growing and pigmented anagen-stage hair follicles were sensitive to hair removal by normal-mode ruby laser exposure, whereas catagen- and telogen-stage hair follicles were resistant to laser irradiation [16]. However, in humans, the efficacy of laser hair removal does not appear to always be influenced by the hair growth cycle [8]. Unlike the animal model, there is enough melanin present in each growth cycle of the human hair follicle to obtain selective damage to the hair.



Fig. 21.4 Vaporization of hair shafts and transient perifollicular erythema and edema are the side-effects desired to occur immediately after hair-removal treatment

21.5.2 Side-Effects and Managements of Complications

Laser hair removal was FDA cleared in l996 and has an excellent safety and efficacy profile. Complications are rare if treatments are done carefully and with the patients' skin type in mind [14].

Laser hair removal is not a painless procedure. Most patients experience some discomfort during and immediately after treatment. A topical or local anesthetic can be used before treatment to reduce this effect. Perifollicular erythema and edema are expected in many patients treated with significant laser fluences (Fig. 21.4). The intensity and duration depend on hair color and hair density. This usually lasts a few hours.

Epidermal damage occurs if excessive fluences are used (Fig. 21.5). It is also more common in patients with a tan. Herpes simplex outbreaks are uncommon but may occur. There is a higher risk among patients with a previous history of herpes simplex and when the perioral, pubic or bikini areas are treated. The risk of bacterial infection is extremely low; However, it may occur following epidermal damage.

Folliculitis may occur in areas treated after excessive sweating or vigorous exercise. An additional risk is posed by swimming, or using a hot tub around treatment sessions.

The most common side-effects are transient pigmentary changes such as hypopigmentation (Fig. 21.6) or hyperpigmentation. It can be prevented if the appropriate treatment fluences are chosen for a certain skin type. This problem is mostly seen in patients with darker skin types or when patients have had a recent tan. Permanent pigmentary changes are unlikely except in dark-skinned individuals.

Scarring is unlikely except in cases of over-aggressive treatment or post-operative infection.

Loss of freckles or lightening of tattoos or pigmented lesions is not uncommon. Patients should be aware of this possibility.

Temporary or permanent leukotrichia has been said to develop following laser or IPL hair removal. This finding may be explained by differences in the thermal relaxation times of melanocytes and germinative cells. The light absorbed and the heat produced by melanin may be sufficient to destroy or impair the function of melanocytes but insufficient to damage the hair follicle cells.

A case of lichen planus being triggered by long-pulsed ruby-laser treatment for hair removal has been reported. Logic would suggest that all patients with a



Fig. 21.5 Incorrect use of treatment parameters (fluence too high for particular skin type) caused epidermal damage with subsequent superficial crusting

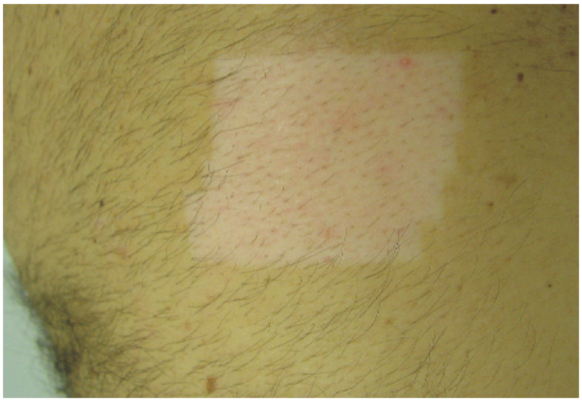


Fig. 21.6 Treatment of recently tanned skin caused hypopigmentation

history of skin diseases known to show an Koebner phenomenon, such as psoriasis vulgaris, vitiligo, lichen planus, and Darier disease, should be informed about this possible adverse effect of treatment; clinically this is rarely seen.

Livedo reticularis (Fig. 21.7), intense pruritus, and urticaria have been reported, including a case of intense swelling and erythema. The pathophysiology of these phenomena is not known. Management included topical corticosteroids, antihistamines, and discontinuing treatment. Several cases of induction of hair growth following laser hair removal in young female patients with darker skin types have been reported. Two different phenomena have been observed: conversion of fine vellus hair to dark, coarse terminal hair at the site of treatment, and induction of the growth of long fine hairs in

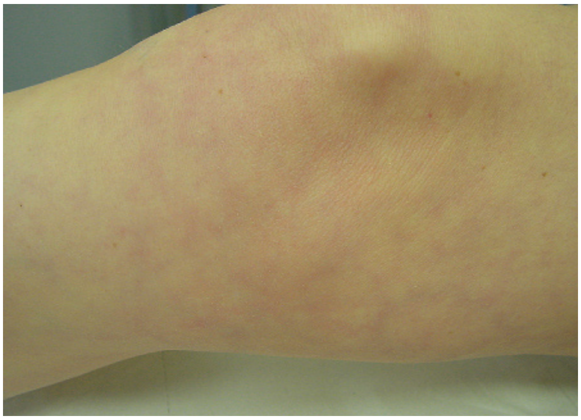


Fig. 21.7 Induction of reticulate erythema on upper leg after a single treatment with a 800-nm diode laser (fluence 50 J/cm²). Note the difference with the lower where no treatment was administered

the immediate vicinity of the treatment area. Repetitive, low fluence treatments with hair-removal devices have also been reported to induce hair growth. Further study is ongoing to assess the mechanisms for this response. Treatment of this side-effect has included continued treatment in some cases.

Light-based hair-removal devices are designed for strong absorption by melanin and deep tissue penetration. These systems are therefore capable of causing retinal injury and proper eye protection must be worn by the patient and operating personnel. Treatment near or on the surface of an eye is not recommended. All other body sites can be treated safely.

The "plume" generated by the vaporized hair shafts has a typical sulfuric smell and in large quantities can be irritating to the respiratory tract. A smoke evacuator is recommended.

21.6 Future Directions

Research has shown that the average long-term hair loss per treatment is about 20%–30%. Multiple treatment sessions are therefore usually required to achieve the maximal level of hair reduction. Attempts have been made to increase the efficacy of each treatment session, in an attempt to reduce the total numbers of treatments. A new FDA-approved patented technology, called Photopneumatic Therapy and developed by Aesthera (Livermore, Calif.), has recently been introduced. It combines the properties of broadband light with pneumatic energy. Photopneumatic Technology results in the elevation of the hair follicle, bringing it closer to the surface of the

skin, while melanin and blood concentration are greatly reduced. As a result, more effective photons should impact the hair follicles, making hair removal potentially more efficient [15].

The role of lasers and filtered flash lamps in hair removal has been determined over the last few years. Several controlled studies have demonstrated the efficacy and safety of light-based hair removal. The procedure is also very attractive because of its non-invasive nature, the ability to cover a large treatment area, and the speed of treatment. Recently, smaller and less expensive light-based devices have become available for self-treatment in home-like environments following instructions and guidance provided by a physician. Studies showed that with adequate training and instruction, patients may administer self-treatments for hair removal with this small light-based unit in a safe and effective manner. Recent studies have shown that continuous-wave, laser systems that emit long laser pulses potentially lead to long-term hair removal after repeated treatments at low energy [17]. This has stimulated research to develop portable, light-based hair-removal devices that women can buy and use at home, rather than having to visit a clinic for treatment.

Summary for the Clinician

Photoepilation has shown unparalleled success. Laser and flash lamp technology now offer the potential for rapid, safe, and effective treatment of unwanted hair. An ever-increasing number of published studies have confirmed the long-term efficacy of laser and flash lamp treatment. The procedure is also very attractive because of its non-invasive nature, the ability to cover a large treatment area, and the speed of treatment. The benefits of this technology were initially mainly limited to individuals with dark hair and relatively fair skin; however, studies with devices with a combination of longer wavelengths, longer pulse durations, and adequate cooling have shown that individuals with darker skin can be treated safely and effectively too. The remaining challenge is to develop the means to eliminate light-colored hair as well. Recent studies have shown that repeated treatments with long-pulsed laser systems at low energy could lead to long-term hair removal. This has stimulated the research to develop portable, light-based hair-removal devices available for self-treatment in home-like environments. If research studies meet the regulatory requirements, product commercialization of these so-called laser-razors could become a reality.

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Chapter 22

Surgical Treatment of Hair Loss

22

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Synonyms

hair transplantation, follicular unit hair transplanting, follicular unit hair transplanting combined with multi-follicular unit grafts ("mixed grafting"), slit grafts, slot grafts, round grafts, alopecia reduction, alopecia reduction preceded by soft tissue expansion, flap surgery

Key Features

- Follicular units have become the basic building block of modern hair transplantation and terminology. The donor tissue harvesting technique has changed enormously in the last 15 years and has revolutionized what can be accomplished with hair transplanting.
- Planning for hair transplanting should consider present as well as future areas of involvement, and one should ideally transplant into areas that are still hair bearing, but that can reasonably be expected to become alopecic in the future. It is not necessary to wait until an area is completely alopecic before starting hair transplanting. The patient can also have the option of spreading transplant sessions over a long period of time, keeping pace with further hair loss, thereby making the cost and inconvenience of transplanting more manageable.
- If follicular units are used exclusively, the results will look totally natural in any area when all of the original hair has been lost.
- A substantial majority of women can also achieve excellent results with hair transplantation. A growing number of female patients are having their hairlines and pre-auricular hair re-established after facial plastic surgery.
- Patients with cicatricial alopecia may be treated with flap surgery or alopecia reduction with or without preceding soft tissue expansion. In addition, hair transplanting can be successfully utilized in such individuals.

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22.1 Introduction

The surgical correction of alopecia may be conveniently divided into three general categories: hair transplantation, alopecia reduction (AR), and flap surgery. Hair transplantation will be discussed under two major subheadings: (1) follicular unit hair transplanting (FUT) and (2) "mixed grafting," a combination of follicular units (FU) and grafts that contain multiple FUs: multi-unit grafts (MUGs). The reader should refer to Table 22.1 for definitions of the graft terminology that will be used in this chapter. Alopecia reduction (AR) can be subdivided into: (1) standard AR, (2) major AR, (3) scalp extension, and (4) AR preceded by soft tissue expansion. It will be dealt with relatively briefly here because of its infrequent use today and space restriction. The last category is flap surgery, which will also be only superficially described here because it is rarely utilized in modern hair restoration. Readers are referred to other sources for a more complete discussion of these procedures [30, 46].

22.2 History

The success of modern hair transplantation depends on a phenomenon first described by Orentreich in 1957 as donor dominance: hair taken from the permanent hair-bearing rim of patients with androgenetic alopecia (donor area) and transferred to non-hair-bearing areas of the scalp (recipient area) will continue to grow in its new site for as long as it would have in the area from which it was taken. Orentreich's observation set the stage for an explosion in the use of corrective surgery for male-pattern baldness and other types of alopecia. It appears though that Orentreich's publication was not the first to deal with the concept of transferring hair from one area to another. The first to successfully show that it was possible to transplant hairy areas – in animals – was Baromio in approximately 1804. Nevertheless, the pioneer in the transplantation of hair from hair-bearing areas to non-hair-bearing surfaces was Dieffenbach, who published in his doctoral thesis in 1822 the use of goose quills as trephines (punches) that were used to bore out hair-bearing pieces of skin, which were then successfully transferred to non-hair-bearing areas. Dieffenbach, however, gave credit for the idea to his teacher, Karl Unger. Afterwards there followed a series of attempts to surgically treat scarring alopecia, but it seems that the contributions of Durham in 1893, Davis in 1911, and Passot in 1931 were the preambles for the work of Okuda. In 1939, Okuda developed a circular scalpel with a diameter of 2–4 mm, which he used to obtain punch samples from hairy areas to transfer them to alopecic areas of the scalp, eyebrows, and mustache. However, Okuda did not use this technique in androgenetic alopecia. To disguise the unesthetic frontal implantation line resulting from Orentreich's original punch graft technique, Marritt present what he called a "practical solution for improving the aspect of the implantation line of hair transplants." Marritt manually separated the follicular units from punch samples using a pair of forceps and a scalpel. When the follicles to be transplanted were separated one by one or two by two, they were known as "micrografts," and when they were transplanted as three to eight units, as "minigrafts." This procedure was quickly adapted, using punch pieces, and later transversal strips taken from the occipital scalp area. Although it seemed that, after Marritt's description, there could be no further advance, since the 1990s several techniques refining the harvesting and placement of these grafts have been developed.

22.3 Technology

22.3.1 Planning

22.3.1.1 Male Patients

Male pattern baldness (MPB) is a progressive disorder. Schematic drawings of different stages/types of hair loss as described by Hamilton/Norwood can be found in Chap 9. Tables 22.2 and 22.3 indicate the frequency of the various types of MPB in men, at different ages, as tabulated in the two largest studies published [22, 43]. Planning for hair transplanting should therefore take into consideration present as well as future areas of involvement, and one should ideally transplant into areas that are still hair bearing, but that can reasonably be expected to become alopecic in the future (Figs. 22.1, 22.2a,b, 22.3a,b). This approach eliminates the need to

Table 22.1 Current graft terminology based on the number of follicular units per graft, the type of recipient site, and whether the graft is cut to be a specific size or to contain a specific number of follicular units or hairs

Graft type	Hairs	FUs	Recipient site	Cut „to size" or cut to „number of hairs"
MICROGRAFTS				
Micrograft – (general term)	1–4	1 or less	Needle / Micro-slit	Cut to „number of hairs"
Follicular unit (FU) – (specific term)	1–4	1	Needle / Micro-slit	Cut to „number of hairs"
Follicular family (FF)	5–6	2	Needle / Micro-slit	Cut to „number of hairs"
MULTI-FU GRAFTS				
Micro-slit grafts				
Double FU (DFU)	3–5	2	Slit	Cut to „number of hairs"
Triple FU (TFU)	5–8	3	"	"
Quadruple FU (QFU)	6–12	4	"	"
Traditional slit grafts				
Small *slit* graft	3–5	~2	Slit	Cut to size
Medium *slit* graft	5–8	~3	"	"
Large *slit* graft	6–12	~4	"	"
Slot grafts				
Small *slot* graft	6–8	~4	Slot	Cut to size
Medium *slot* graft	8–12	~6	"	"
Large *slot* graft	10–16+	~8	"	"
Round grafts				
Small *round* graft	5–8	2–3	Punch	Cut to size
Medium *round* graft	8–14	4–5	"	"
Large *round* graft (includes standard punch grafts)	14–30+	6–15+	"	"

constantly "chase" an enlarging area of alopecia, and leaves the patient with a long-term naturally occurring hair growth pattern. The "price" for this operative philosophy is that a smaller proportion of the obviously thinning areas can be transplanted during each surgery – unless one employs more grafts. In the long run, the advantages of concomitantly transplanting future areas of loss become evident.

It is important to at least briefly address the implications of finasteride treatment in planning. In clinical studies, finasteride has been shown to be very effective in slowing hair loss in the vertex area (88% of patients), and somewhat effective in the mid-scalp area (60% of patients) (Fig. 22.1). Indeed, 66% of patients also had some regrowth of hair in the vertex area, and 39% had some regrowth in the mid-scalp area [13]. However, there is no scientific evidence that finasteride can be depended upon to *permanently* stop the progression of MPB. To the contrary, even in patients who grow more hair in response to finasteride, hair counts begin a

Table 22.2 Unger's study on the incidence of different types of male pattern baldness in 268 men 65 years or more [35]

Type	Age (years)			
	65–69[a]	70–74[b]	75–79[c]	80+[d]
I	2 (3.6%)	5 (6.2%)	4 (5.5%)	2 (1.7%)
II	9 (16.4%)	7 (8.6%)	7 (9.6%)	12 (10.1%)
III	4 (7.3%)	15 (18.5%)	18 (24.7%)	11 (9.2%)
IV	10 (18.2%)	16 (19.8%)	8 (11.0%)	10 (8.4%)
V	6 (10.9%)	7 (8.6%)	10 (13.7%)	16 (13.4%)
VI	13 (23.6%)	19 (23.5%)	16 (21.9%)	37 (31.1%)
VII	11 (20.0%)	12 (14.8%)	10 (13.7%)	31 (26.1%)
Total	55 (100%)	81 (100%)	73 (100%)	119 (100%)

[a]In age group 65–69 if one excludes type I and II, 33 of the remaining 44 (75%) have types III–VI (83.3% Norwood).
[b]In age group 70–74 if one excludes types I and II, 57 of the remaining 69 (82.6%) have types III–VI (82.8% Norwood).
[c]In age group 74–70 if one excludes types I and II, 52 of the remaining 62 (83.9%) have types III–VI.
[d]In age group 80+ if one excludes types I and II, 74 of the remaining 105 (70.5%) have types III–VI (74.0% Norwood).

Table 22.3 Norwood's study on the incidence of male pattern baldness in 1000 men by type and age [22]

Type	Age (years)						
	18–29	30–39	40–49	50–59	60–69	70–79	≥80
II	52 (28%)	43 (26%)	38 (22%)	32 (20%)	24 (16%)	20 (19%)	11 (14%)
III	14 (6%)	30 (18%) (3V)[a]	37 (20%) (15V)[a]	34 (23%) (15V)[a]	22 (15%) (10V)[a]	16 (16%) (7V)[a]	12 (16%) (8V)[a]
IV	4 (3%)	16 (10%)	15 (10%)	21 (9%)	17 (12%)	13 (13%)	9 (12%)
V	3 (2%)	10 (6%)	13 (8%)	15 (10%)	22 (15%)	13 (13%)	9 (12%)
VI	2 (1%)	4 (3%)	7 (4%)	10 (7%)	19 (13%)	11 (11%)	10 (13%)
VII	0 (%)	2 (1%)	5 (3%)	4 (3%)	16 (10%)	11 (11%)	14 (17%)
Total	185 (100%)	165 (100%)	165 (100%)	156 (100%)	149 (100%)	102 (100%)	77 (100%)

[a]*Numbers* in *parentheses* under type III represent type III vertex individuals.

steady decline after the second year of treatment. Long-term (lifetime) planning should therefore not be predicated on the assumption that finasteride is a permanent "cure" for MPB. However, finasteride does delay the development of vertex and, to a lesser extent, mid-scalp alopecia in many patients. This allows us to concentrate our initial transplanting on frontal and mid-scalp areas as shown in Fig. 22.1, and to encourage patients to try a 1-year course of finasteride for any vertex hair loss before committing to surgery at that site. Because perfect prognostication of the degree of alopecia that any given patient will develop is impossible, it is also wise to maintain a donor area "reserve" of what is expected to be permanent hair – especially in younger individuals. In addition, the lateral borders of the transplanted areas should be constructed with FU, so if one misjudges the

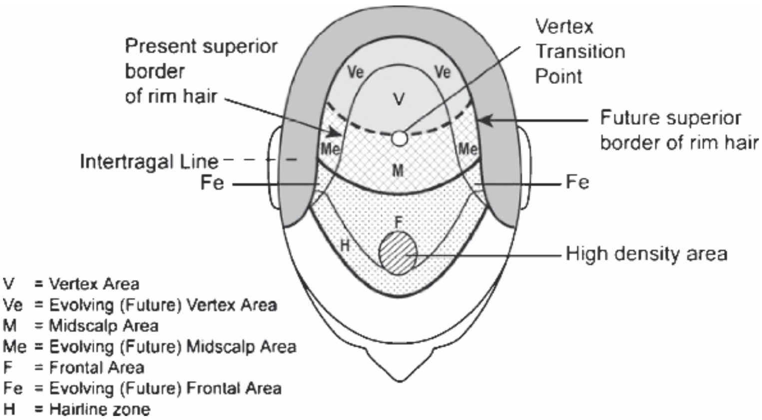


Fig. 22.1 A schematic drawing showing frontal, mid-scalp and vertex areas, as well as evolving areas of male pattern baldness (*MPB*) in a patient with types V to VI MPB. Ideally, each of the three major areas is treated at the same time as the evolving areas of MPB lateral to them. Typically, only one major area and evolving area are treated during each session. Re-creating "temporal humps," as shown, allows us to place the lateral points of the hairline more superiorly on the humps than would otherwise be possible. This has the effect of decreasing the antero-posterior length of the frontal area while maintaining a cosmetically advantageous horizontal orientation to the hairline, when it is viewed laterally

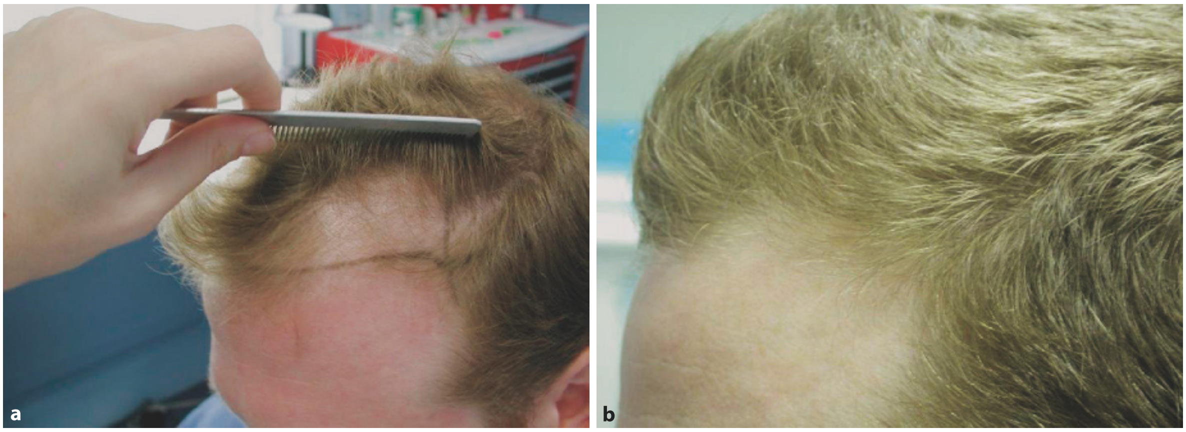


Fig. 22.2 **a** A 32-year-old male patient before transplanting with moderately advanced hair loss. **b** The same patient 9 months after a session consisting of 1625 follicular units (*FU*). Starting transplanting at earlier stages of hair loss is advantageous in that postoperative camouflaging of the grafting is easier, there is less obvious alteration of the appearance to friends and associates, and the patient avoids going through the embarrassment of ever being totally alopecic. (Photos courtesy of Dr. Robin Unger)

ultimate limits of MPB, the patient will be left with a larger than usual isolated frontal forelock (IFF) which will look "natural" standing on its own [2].

It is not necessary to wait until an area is completely alopecic before starting hair transplanting. In fact, starting at earlier stages of hair loss is advantageous in that postoperative camouflage of the grafting is easier, there is a less obvious alteration in appearance to friends and associates, and the patient avoids going through the embarrassment of ever being totally alopecic (Fig. 22.2a,b). The patient can also have the option of spreading transplant sessions over a longer period of time, keeping pace with further hair loss, thereby making the cost and inconvenience of transplanting more manageable. If FU are used exclusively, the results will look totally natural after a single session in any area when all of the original hair has been lost (Fig. 22.3a,b).

22.3.1.2 Female Patients

Although many females thin in a "male pattern" of enlarging fronto-temporal triangles and/or have a thinning "vertex" area, female pattern hair loss (FPHL) usually



Fig. 22.3 **a** A patient before his first transplant. The black crayon marks denote the perimeters of the areas to be transplanted. Note that the transplanting is intended to include areas that are still hair-bearing, but that can reasonably be expected to become alopecic in the future. **b** The same patient 9 months after the second of two follicular unit transplants (*FUTs*). The first one consisted of 1784 FU and 231 double FU to the frontal area and the second of 1849 FU to the mid-scalp area. If FU are used exclusively, the results will look totally natural after a single session in any area when all of the original hair has been lost

takes a different form than MPB. Olsen describes these patterns in Chap 10. Maintenance of at least some hair in the hairline zone, thinning posterior to the hairline zone, as well as small 1- to 2-mm round and irregularly shaped alopecic areas that are scattered throughout the diffuse thinning are all hallmarks of FPHL [23]. In addition to thinning over the caudal scalp, a significant *minority* of women also develop thinning in the usual occipital donor areas. The women in this minority are not good candidates for hair transplantation. However, as will be discussed below, in the authors' opinion, a substantial majority of women can achieve excellent results with hair transplantation (Fig. 22.4a,b) [42].

The most important aspect of planning in female patients is to decide which regions, if thickened, would provide the greatest cosmetic benefit. Those areas should be transplanted first. In many females the most important area is the frontal caudal region and in some it is a pre-determined part-line. Thus, transplanting is often limited to a cosmetically strategic 7.5- to 10-cm-wide midline corridor, extending from the hairline zone as far posteriorly as is necessary and possible, given the reality of limited donor reserves; the hair in this thickened corridor is subsequently combed in such a way as to produce the most effective coverage of areas that cannot be treated because of the latter. Provided that there are sufficient donor reserves, thinning or alopecic fronto-temporal triangles can also be transplanted. It should be remembered, however, that some degree of thinning fronto-temporal triangles occurs in 79% of post-pubertal females and type IV MPB occurs in respectively 25% and 50% of 50-year-old and 60-year-old otherwise normal women [8]. Using grafts to treat such areas depletes the limited donor reserves that may later be needed to treat less easily camouflaged areas of hair loss. A growing number of female patients in our office are having their hairlines and pre-auricular hair re-established after facial plastic surgery (Fig. 22.5a,b). There may be other areas of thinning that the patient wants to treat, and provided there is sufficient donor hair, these may be addressed in later surgeries. Again, for most patients it is wise to leave enough hair in the donor region to treat unexpected future areas of loss.

22.3.1.3 The Hairline

In males, the hair restoration surgeon (HRS) needs to decide whether the "supratemporal humps" consist of permanent hair or whether, most commonly, they need to be re-created or reinforced with FU. The midline point of the hairline should usually be located so that when the hairline is completed and is viewed laterally, it runs more or less horizontally. In addition, the anterior most point of the hairline zone ideally lies in a transition area within which the vertical aspect of the forehead becomes more parallel to the ground. Most hairlines are designed in a "bell-shape" which, together with the aforementioned anterior midline point and reconstructed or permanent "temporal humps," allows the lateral points to be placed more superiorly on the humps. All of the foregoing has the effect of decreas-



Fig. 22.4 **a** A female patient with thinning in the frontal area before transplantation. **b** The same patient 9 months after a single session to the involved area. The improvement in hair density shown is typical of a single FU transplanting session to an area of thinning

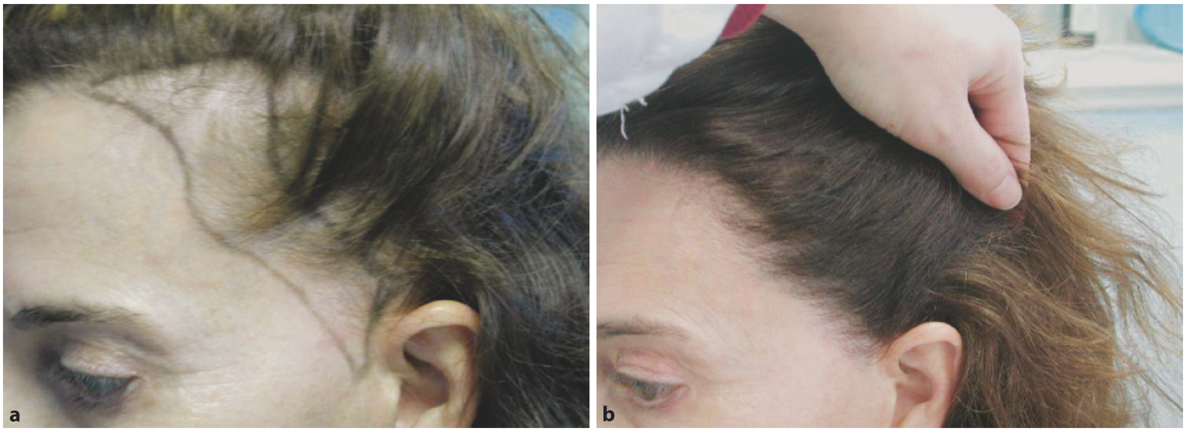


Fig. 22.5 **a** A female patient approximately 2 years after a rhytidectomy which resulted in the temporal and preauricular hair being lifted superiorly and posteriorly. The patient wanted to have hair-bearing areas back where they were prior to the face-lift. **b** The patient 1 year after a single session of 1252 micrografts. A growing number of female patients in our office are having their hairlines and preauricular hair re-established after facial plastic surgery. (Photos courtesy of Dr. Robin Unger)

ing the antero-posterior length of the frontal area, while still maintaining a cosmetically advantageous horizontal orientation to the hairline [41] (Figs. 22.1, 22.2). In females, the hairline is flatter, with minimal fronto-temporal recessions and is usually created just posterior to the existing hairline, which often becomes significantly sparser with the passage of time [42].

Natural hairline zones have the following characteristics: (1) an irregular anterior border, (2) irregular hair density, (3) fine hair most anteriorly, becoming coarser as one moves more posteriorly, (4) often single fine textured "sentinel" hairs scattered irregularly anterior to the bulk of the hairline zone, and (5) changing directions and angles of the hair [25, 28]. Transplant surgeons should of course try to mimic these characteristics (Figs. 22.2b, 22.3b, 22.5b).

22.3.1.4 Alopecia Reduction

Alopecia reduction (AR) is defined as the excision of an area of alopecia or future alopecia, in a single or series of procedures. Because of improper planning and/or inadequate surgical skill, many patients have been more hurt

than helped by the employment of AR in their hair-restoration treatment plan. Such unfortunate results have received widespread attention and the popularity of AR has therefore plummeted to the point where it is rarely used today. Nevertheless, if it is planned and executed, it can be very useful [20, 31]. Alopecia reduction will be briefly discussed elsewhere in this chapter but some admonitions and comments on its role in planning are warranted here:

- If the transplanting goal is maximum coverage, the surgeon should ideally consider the use of AR or plan to use AR in the future by leaving un-transplanted zones that can be excised at a later date.
- Do not leave a scar in an area that you do not intend to subsequently transplant.
- Do not try to excise *all* of the alopecic area. This will result in an abnormal hair direction at the midline, which has been referred to as the "parting of the Red Sea" effect. For example, if one eliminates all but a 5- to 6-cm-wide area of alopecia, this remaining area can be transplanted with grafts that produce a natural looking gradual change of hair direction from left to right or right to left.
- The wider the area of alopecia that is removed, the sparser the hair in the stretched "permanent" fringe will become. Fringe hair will also gradually become sparser with age, and this should be factored into objectives for AR; despite arguments to the contrary, if the patient has normal healing, this is the only negative consequence of AR that is not completely avoidable.
- In the vast majority of patients, if surgical technique is good, there is minimal "stretchback" or loss of some of the gain obtained [20, 31]. More recently, the use of non-absorbable galeal "anchoring sutures" has further minimized this potential sequela of AR [21].
- AR is a very useful tool for the treatment of MPB that has extended beyond its originally estimated borders. It is generally unwise to expend a limited supply of remaining donor tissue to treat what were unanticipated new areas of alopecia if those areas could instead be excised [32].

22.3.2 Preoperative Instructions and Anesthesia

Our patients are given detailed preoperative instructions including a variety of measures that may help to reduce excessive intra-operative and postoperative bleeding: 3 weeks prior to surgery they are directed to stop ingesting vitamin E, and any herbal preparations known to increase bleeding. Patients are also told to discontinue acetylsalicylic acid and avoid any consumption of alcohol for 1 week prior to surgery. Other medications regularly used by the patient, which might cause complications or increase bleeding, should also be discontinued for an appropriate time before surgery [34]. In our office, an optional homeopathic regimen, consisting of arnica, bromelain, and vitamin C, is started 2 weeks preoperatively. Although evidence to support the use of these agents is largely anecdotal, many physicians feel the regimen improves healing, speeds recovery, and minimizes swelling. The authors also give their patients a preoperative intramuscular injection of prednisolone acetate (Depomedrol) 8 mg and a tapered, 6-day postoperative course of prednisone starting the day after surgery (30–25–20–15–10–5 mg/day). Perioperative prophylactic antibiotics are prescribed – usually cefdinir (Omnicef) 300 mg – one capsule 1 h before surgery and one 6 h later. The hair is shampooed the night before and the morning of the transplant.

Personal and family medical histories are taken to rule out any contraindications to surgery. All of our patients have a complete blood count (CBC), and VDRL (Venereal Disease Reference Laboratory), human immunodeficiency virus (HIV), as well as hepatitis B and C antigen tests prior to beginning treatment. These tests are repeated yearly should the course of treatment extend over more than a 12-month period. Although we do operate on individuals with both HIV and hepatitis, extra precautions are taken, including obtaining medical clearance from the treating physician. It also allows our team to protect themselves with *immediate* prophylactic treatment in the case of accidental exposure.

Diazepam (Valium) 20 mg is given orally 30 min before surgery to minimize anxiety but more importantly to decrease the possibility of anesthetic toxicity [1]. In addition, the patient is given dihydrocodeine and paracetamol (Vicodin®) to minimize the discomfort of the initial injections. The donor area is anesthetized by raising individual wheals along the inferior edge of the proposed excision area, using a solution of 2% lidocaine with 1/100,000 epinephrine. This solution is prepared on the morning of surgery to minimize the "stinging" associated with the more acidic pH of the stock solutions that are pre-mixed with epinephrine. After waiting for approximately 2 min, these wheals are then extended laterally in both directions, via needle entries into the already anesthetized areas, until these sites meet one another, thus producing a complete field block with minimal discomfort to the patient [38]. Occasionally it is necessary to reinforce "hot spots" with lidocaine 3% or 4% with 1/50,000 epinephrine and some patients require additional anesthesia of the superior donor zone edge (usually individuals who have had prior hair res-

toration surgery). Approximately 6 ml of 1/50,000 epinephrine is added to the donor area, superior to the field block to produce additional hemostasis.

Once the donor area has been harvested and sutured, three injections of 2% lidocaine with 1/100,000 epinephrine are made along the proposed hairline with a 30-G needle – one in the midline and one in the middle of the proposed left and right hairline. These wheals are extended to complete the field block, with minimal discomfort, much in the same manner as described above for the donor area. If this is done slowly enough, the patient only feels the initial three injections. If patients are known to be particularly difficult to anesthetize, the field block is accomplished with the use of 3% or 4% lidocaine with 1/50,000 epinephrine. Then 15–30 min after completion of the recipient area field block, the recipient region is intermittently infiltrated superficially with epinephrine 1/50,000 to minimize intraoperative bleeding. A total of 10–20 ml of the epinephrine will be used *intermittently* and in *small* doses to provide improved hemostasis throughout the recipient area during the course of treating it.

The field blocks are reinforced approximately every 3 h or as needed, with 2%–4% lidocaine with 1/50,000 epinephrine or with bupivacaine (Marcaine) 0.05% with 1/200,000 epinephrine. At the end of the procedure the donor area anesthesia is reinforced again – this time always with the bupivacaine – and an intramuscular injection of Ketorolac tromethamine (Toradol®) 30–60 mg is usually administered. It eliminates virtually all postoperative pain in most patients for 3–5 h. It should not be used in patients with a history of asthma or gastrointestinal ulcers. A single dose of Toradol® has never been reported as causing acute glomerulonephritis – one of its most serious potential complications. It has been used in over 4000 of our surgeries and has not produced a significant increase in postoperative bleeding.

Propofol, administered by an anesthesiologist, can also be employed in individuals who are very apprehensive about "needles" or who require usually large amounts of anesthetic solutions. In these cases, both donor and recipient area field blocks can be completed quickly, while the patient is unconscious for a short time.

22.3.3 The Donor Site

The donor tissue harvesting technique has changed enormously in the last 15 years and has revolutionized what can be accomplished with hair transplanting. In brief, the donor area is maximally tumesced with saline, before a rectangular strip with tapered ends is excised from the densest area of the donor rim – usually midway between its superior and inferior borders. This tissue is excised with a double-bladed scalpel held at the same angle as the hair exiting the scalp. The width of the strip is primarily determined by scalp laxity, which varies from patient to patient and within the same patient from one area to another, as well as from one surgery to another. Once it is removed, the donor site is closed with a 2-0 Supramid suture – most often in a single layer. The author always takes a slightly *narrower* strip than he thinks is possible with any degree of scalp laxity, thereby allowing for a margin of error [43]. This helps to ensure that there is no tension upon closure, and increases the likelihood of a narrow donor scar – typically 0.2–1.5 mm wide in his practice. Occasionally, wider scars occur and there are several probable causes: (1) healing characteristics intrinsic to the patient, (2) excessive tension upon wound closure, (3) poor blood supply, most commonly seen in "repair" patients who have multiple rows of scar tissue superior and/or inferior to the new excision site, (4) excessive wound tension *after* closure, secondary to severe postoperative edema, (5) *extreme* laxity in the donor region – usually corrected by leaving the sutures in place for at least 2 weeks postoperatively.

After the first surgery, all subsequent donor strips will include the scar from the prior harvest(s). Thus, no matter how many sessions are carried out, only a single narrow scar is ever present. If the patient had surgeries previously, with older methods of harvesting that left multiple scars, it is usually possible to excise two rows of scars within the new donor strip and convert them into a single fine scar while obtaining a considerable amount of the hair between the scars at the same time [45].

Figure 22.6 is a schematic drawing of the potential "permanent" donor zone past the age of 65 years that contains hair density of eight or more hairs per 4-mm circle. It was created from the measurements obtained in a study of 268 elderly men [35]. This zone averages 69 mm high in the midline of the occipital area in at least 80% of such patients, so a substantial "margin of error" is still present if even 60 mm is eventually excised from this area in the form of, for example, six 10-mm-wide strips. In the parietal area, the "permanent" donor area is on average 80 mm high. In addition, potential donor sites with fewer than eight hairs per 4-mm circle superior and inferior to this area can be utilized if necessary.

Note that the permanent donor zone is widest in the parietal areas so elliptical excisions should ideally *not* have their widest aspects in the midline of the occipital area, as is too commonly seen. It is also important to recognize that the measurements obtained in the above-quoted study were obtained from non-tumesced potential donor areas. When strips are harvested from tumesced tissue the donor area has been stretched by the tumescent fluid so, for example, an ostensibly 10 mm strip actually represents the removal of less than 10 mm of non-tumesced tissue.

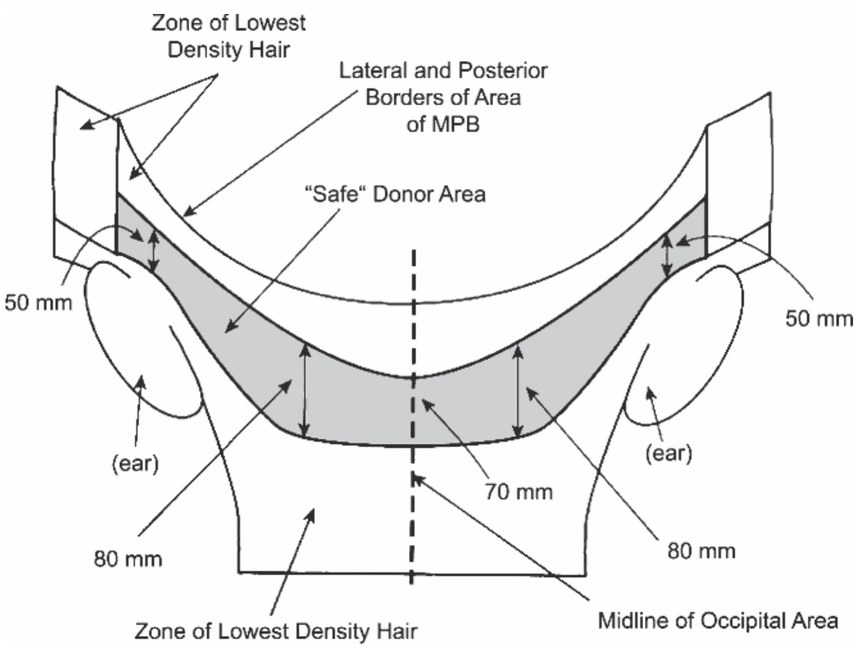


Fig. 22.6 Above is a schematic drawing of the potential "permanent" donor zone that contains hair density of 8 or more hairs per 4-mm circle in male Caucasian patients older than 65 years. It was created from the measurements obtained in a study of 268 such men [35]

Once the strips are carefully removed from the donor sites, any larger bleeding vessels are cauterized with a Hyfrecator set at unipolar delivery and 80-90. The wound is usually closed with a running, relatively superficial, single-layer suture technique using Supramid 2-0 with a CL30 needle. Loops are normally placed 4–6 mm apart. If there is any tension on closure, one can use interrupted sutures and/or galeal sutures and/or undermine the superior flap, in that order of preference. The length and width of the donor strips, closing tension (rated from 1 to 10) and the numbers and types of grafts obtained are noted on the operative record as a guide for future sessions.

A recent and sometimes useful innovation in harvesting donor tissue has been referred to as follicular unit extraction (FUE) [24]. A small-bore trephine – usually 1 mm or less in diameter – is used to incise around an individual FU to an approximately mid-dermis level. The FU is then gently eased out of its site with a combination of (1) traction and (2) pressure with a blunt trephine [9], or peripheral 27-G needle punctures [44] intended to sever its fibrous attachments. It is an advantageous technique for special circumstances, such as for patients who prefer to avoid a linear scar (no matter how narrow it might be), those who are prone to develop wider than normal scars or who have such scars from prior hair transplanting, for patients with tighter than average scalps, and those who have no further donor strip sites left. Unfortunately, this method of harvesting currently has several significant problems associated with it [44]. A small group of HRS is working on these issues, but the authors cannot recommend its routine use in *most* individuals *at this time*. Its refinement, however, is continuing and involved practitioners are even investigating the use of body hair for scalp hair transplantation – thus possibly providing additional donor hair reserves in some patients.

22.3.4 Graft Preparation

Hairs emerge from the scalp as single hairs or, far more often, in small groupings of two, three, and less commonly four or five closely associated hairs [10]. These "follicular groups" or "follicular units" have become the basic building block of modern hair transplantation and terminology (see Table 22.1). Bobby Limmer [16] was the first HRS to realize the clinical importance of FU in hair transplanting and, as indicated, his approach has been widely adopted or modified as will be discussed below.

For FUT, the donor strip is first carefully divided into narrow slices or "slivers" using super sharp razor blades much as one would slice a loaf of bread. These slices are one or two FU wide and are prepared with six to ten times magnification so as to ensure this limited width and avoid FU transection. Then a small jeweler's forceps and the razor blades are used to section the tissue into pieces containing the desired numbers of FU or hairs. A small amount of subcutaneous tissue is left below the

level of the deepest hair bulbs. Grafts ideally should be grasped by this subcutaneous "tag" when they are being inserted into recipient sites. The rest of the alopecic skin and subcutaneous tissue is sectioned off the grafts as part of the "cleaning" process. The author prefers a "pear-shaped" graft with limited tissue at the epidermal end and more tissue to cushion the bulb area at the proximal end of the grafts.

The strip must be kept constantly moist, and, after separating the grafts from the strip, the author's technicians place them in sterilized ceramic escargot dishes filled with saline. The individual "wells" of the escargot dishes are labeled according to hair color, as well as the number and caliber of hairs in the grafts, in order to simplify and organize the later process of graft placement (see below). They are kept cool by placing the escargot dishes on a "Lepaw graft cooler" (A to Z Surgical Supplies) – a Pyrex dish filled with ice.

If "micro-slit" grafts are being employed, possible "compression" of hair into dense unsightly lines is eliminated by making them only one FU wide and two to three FU long. "Slot" grafts are prepared from "slivers" that are two FU wide and three FU long. Grafts that are intended to fill holes made with 1.3–2.0 mm punches are prepared by slicing the donor tissue into 2 mm^2 grafts, and those that will be inserted into holes made with 3.0–3.5 mm punches are generally 3.5 mm^2 in size. The multi-follicular unit grafts (MUGs) are tested in the recipient sites to be certain their size is appropriate – placement should result in a "snug" fit, but not so tight as to produce compression of the hair within the graft.

The less one injures follicles during graft preparation the better. With the exception of dehydration, however, it appears that a great deal of abuse must be administered to the follicle to actually impair hair growth [7]. Even intentional mutilation of follicles will often not deter growth. Kim and Choi have, for example, demonstrated 80% regrowth of hair when the distal third of the follicle has been intentionally totally removed [14]. (If the proximal third is removed hair survival drops to 60%.) Limmer [15, 16] has shown somewhat lower rates of hair survival with similar injuries while Mayer [19] has demonstrated that when follicles are divided into distal third and proximal two-thirds and all of the fragments are transplanted, one can achieve a total of 133 hairs from every 100 hairs transplanted (though these hairs usually have a finer texture). Regardless of the variable percentage rates of survival, it is clear that substantial damage can be done to follicles without death of the hair and that our instinct for preserving intact FU *may* be more emotional than necessary. Minor follicular injuries during graft preparation appear to be far less important than, for example, excessive handling/dehydration of FU during "dense packing" (see below).

Some unseen telogen follicles can be mistakenly discarded as part of the "garbage" between FU when microscopic dissection of donor tissue is used to remove everything but the visible anagen hairs in FU [37]. Studies which have shown 33% more hairs growing than were originally counted, when "chubby" rather than "skinny" FU were transplanted, lend credence to this fear [3]. It would seem wise when producing FU to leave a cushion of tissue around each FU rather than to make them as "skinny" as possible, in order to facilitate their insertion into smaller holes, which in turn facilitates "dense packing."

As noted earlier, we find it useful to segregate grafts into groups that contain, for example, fine hair, higher caliber hair, gray hair, and so on, and then further segregate them according to the number of hairs they contain. By sorting grafts in advance, the ideal graft for any particular recipient site is immediately available to the technician during implantation. Even slight increases in hair caliber can have a marked effect on perceived hair density or hair "bulk." Cole has pointed out that a 0.01 mm increase in average hair diameter can produce a 36% increase in hair volume [5]. This latter fact explains the sometimes remarkably "full" look achieved with FUT in some patients despite relatively low numbers of hairs per square centimeter.

22.3.5 The Recipient Area

A presenting or potential type V to VI MPB is conceptually divided into four zones: the frontal (F), mid-scalp (M), vertex (V), and future areas of loss of each of the three aforementioned regions (Fe, Me, and Ve respectively) (Fig. 22.1). The frontal area extends from the hairline to a modified coronal line drawn perpendicularly from the left and right tragus. The vertex ("crown") area begins at a point that Beehner has called the "transition point" [4], where the more or less flat caudal aspect of the skull starts becoming more vertical, and extends postero-inferiorly to the limits of the alopecic area. The mid-scalp lies between the frontal and vertex areas. If hair is transplanted as far posteriorly as the "transition point," the individual will look as though he has full coverage when viewed frontally and almost full coverage when viewed laterally, despite the presence of an untransplanted bald "crown." In most patients with types V to VI MPB, one session in the F/Fe area and one in the M/Me area will produce very acceptable cosmetic results (Fig. 22.3). If the patient is certain – or nearly so – that he will be agreeing to an AR at some time during the course of treatment, then the potential recipient area of a type V MPB patient is usually conceptually divided into three rather than four zones: the anterior and

posterior halves and the future areas of loss. Patients who are destined to develop less than type V MPB can often be similarly conceptualized as having the same three areas (but without AR), while planning for those who are destined to develop more than types V to VI MPB may have to be dealt with on the basis of five or six zones. In general, one should not attempt to transplant the entire ultimate area of MPB, unless the patient is willing to undergo AR at some point during the course of treatment. Exceptions to this general rule include older patients whose extent and pattern of hair loss are more certain than in younger individuals; those who are seeking relatively less dense coverage of larger areas; and those with exceptionally good prognoses based on family history and physical examination. Even in the latter group, acceptance of perhaps less dense coverage should be anticipated as a possible necessity.

For the majority of patients in whom AR will not be used, limiting transplanting to the frontal and mid-scalp areas is a more reasonable and cosmetically very acceptable goal. The posterior border of the mid-scalp should be completed with FU in a posterior "hairline zone" fashion and should be curved so as to leave a normal, oval, or round shape to the remaining alopecic "crown" area. Despite the foregoing, occasionally patients present with large current or future areas of alopecia and the authors have opted to transplant the *periphery* of the entire vertex area in order to create a "bald spot" in a natural-looking more caudal position. Such peripheral vertex transplantation (PVT) (Fig. 22.7a,b) is utilized when a patient's inferior vertex border is especially low and donor tissue reserves are not sufficient for transplanting the entire vertex area but are adequate for this more limited goal.

As noted earlier, the recipient area can be transplanted in one of two general ways: (1) exclusive FUT, (2) a combination of FU and different types of multi-FU grafts (MUGs). Time and space allow for a discussion of only FUT. A mixture of FU and MUGs will only be addressed briefly but can produce extraordinarily dense looking results (Figs. 22.8a,b, 22.9a,b). Details on this approach can be obtained elsewhere [46].

22.3.5.1 Follicular Unit Hair Transplanting (FUT)

Approximately, 99% of the author's patients and 100% of the patients of most HRS are currently treated with FUT. As techniques have improved, FUT's initial disadvantages have been overcome and its cosmetic efficacy has increased dramatically. As noted earlier, the goal of FUT is to divide the entire donor strip into FU, discarding what is viewed as excess alopecic tissue between the FU. The FU are then inserted into small holes or incisions made by various-sized needles or small blades, thus attempting to re-create what occurs in nature. While FUT can produce remarkable results in relatively early stages of MPB (Fig. 22.2), one of the great advantages of FUT is that a single session can stand completely on its own, looking natural in an area that is totally alopecic or that is destined to become alopecic. Thus, a larger proportion in any area of alopecia that might develop can be treated by transplanting each area only one time. In contrast, if MUGs are utilized each area must be treated *at least* twice in order to produce natural-looking coverage. It also obliges one to consume at least twice the amount of the limited donor tissue reserves to satisfactorily transplant that area. For most alopecic patients, the ability to avoid this, as well as the temporary but possibly noticeable MUGs between the first and second sessions (in the same area) is more important than the somewhat denser result that can be produced with MUGs. As noted earlier, an additional important attribute of FUT is that if the MPB extends beyond your initial prognosis, the then isolated transplanted area will be transformed into a natural-looking IFF.

One of the initial concerns with FUT was that the density that could be achieved was limited because of technical difficulties in closely spacing the sites and/or because of poor growth [15, 18, 37]. The former issue has been resolved with time, practice, and new instrumentation. The latter problem is not a significant issue in offices with experienced physicians and technicians who pay close attention to detail. Better ways of preparing and inserting grafts have evolved, and have resulted in improved survival of hair, despite increasing densities of FU per square centimeter. It is technically very difficult to conduct scientifically valid hair growth studies when dealing with large numbers of small grafts. How, as the result of several small "studies," the author believes excellent growth can be achieved if: (1) FU are handled carefully, follicles are not transected, and grafts are kept constantly moist or totally immersed in a holding solution; (2) each session does not exceed approximately 2500 FU, to limit the number of incisions and damage to the blood supply of the recipient area; and (3) the recipient sites are not spaced any more closely than 30–35 FU/cm^2, again to preserve the integrity of the blood supply to the grafts. It may be possible to obtain good hair survival with larger sessions ("megasessions") and higher densities of FU/cm^2 ("dense packing") but thus far, no hair survival studies have been done that confirm the efficacy of such parameters.

Follicle units containing single hairs are used most anteriorly, two to three rows deep with the finest hairs





Fig. 22.7 **a** Some patients present with large current (as shown above) or future areas of vertex alopecia. Because there is an inadequate supply of donor tissue to transplant the entire vertex, some of them can be satisfied by transplanting the periphery of the vertex area in order to create a "bald spot" in a more natural-looking more caudal position. **b** The same patient as in (**a**), 9 months after a single session of 1805 FU to the periphery of the bald vertex. The remaining area of alopecia is now located in a more aesthetically pleasing, more caudal position

first, and, as already implied, at a density of approximately 30 FU/cm². The recipient sites are made with a 19-G to 21-G needle to allow for easy graft insertion while minimizing vascular damage. F.U. containing two hairs are transplanted for two to three rows posterior to the single-hair FU and at initially similar or slightly higher densities. As one moves progressively more posteriorly, the FU density per square centimeter decreases slightly and FU with more than two hairs are utilized; the sites for these slightly larger grafts are usually made with an 18-G needle. We and many FUT proponents also treat an anterior midline oval zone, "the egg," with FU containing three or more hairs [29] at a density of approximately 30–35 FU/cm² (Fig. 22.1).

The author uses FUT in: (1) the anterior hairline zone in all patients (all of the hairlines in the photos shown in this chapter were created with FU); (2) patients who have sparse temporal hair and/or are aiming for less than high density; (3) *most* patients who present with totally alopecic recipient areas, and (4) patients whose goal is to cover the majority of their alopecic areas.

Creating good tissue turgor is as important in the recipient area as it is in the donor area if you are to minimize injury to hair adjacent to the recipient sites being prepared during any given session. A secondary advantage of tissue infiltration in grafted areas is that once the fluid dissipates the grafts will move closer together and a higher density will be produced. Good control of bleeding in the recipient area is likewise an important component of good hair transplanting. The more bleeding present during the actual surgery the more difficult it is to create recipient sites in an optimal fashion and to insert the grafts with minimal handling and dehydration. Periodic additional infiltration of small amounts of a 1/50,000 concentrat epinephrine is therefore utilized by the author whenever bleeding becomes problematic during preparation of recipient sites and/or graft placement.

One of the most important factors contributing to a natural final result is the angle and direction of the transplanted hair (Figs. 22.2, 22.3). If recipient sites are made too acutely, leading to hairs that are "standing straight up" or that do not mimic the existing flow of hair in any way, the transplant looks artificial, regardless of the size of the grafts utilized or the density of the transplanted hairs. We quite frequently spend 60–120 min just making 1500–2500 recipient site incisions. Making these sites at the correct angle and direction also avoids possible lethal injury to any existing hair in the area. The more pre-existing hair, the more important correct angling and direction becomes.

22.3.5.2 FUT Combined with MUGs

As indicated earlier, approximately 1% of the authors' male patients are treated with MUGs in combination with FU in the frontal area. Space does not allow for a full discussion of the various options and purposes of such combinations but a complete description is avail-

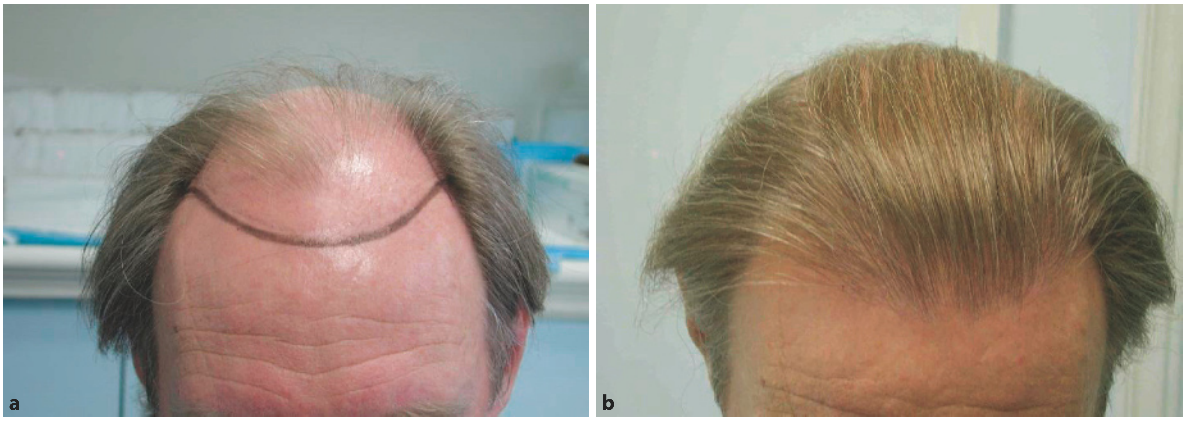


Fig. 22.8 **a** This patient with an excellent donor/recipient area ratio and relatively dense temporal hair wanted denser hair growth in the frontal area than can usually be produced using FU exclusively. He agreed to undergo two sessions 5 months apart using a combination of FU, double FU, and "slot" grafts. **b** The same patient 9 months after his second session. This type of hair density cannot be produced with 2 FUT sessions unless the FU are placed closer together than the authors feel is acceptable for optimal hair survival (see text). The option of grafting with multi-unit grafts is reserved for only a small percentage of the authors' patients whose long-term donor/recipient area ratio is excellent, and whose temporal hair is also expected to remain fairly dense over the long-term

able elsewhere [36, 39, 46]. The decision to use "mixed grafting" is preceded by a careful examination of the patient, discussion of the family history, and a clear explanation to the patient of the "pros and cons." In brief, the patient should have favorable hair characteristics for transplanting, an excellent long-term donor/recipient ratio, some existing hair in the frontal region (to minimize any temporary noticeability of the MUGs) and the ability (both financial and time) as well as determination to do two to four surgeries in the frontal zone. The main benefit of using mixed grafting is that, in our hands, higher densities can be achieved than with FUT alone, without compromising the naturalness of the final result (Figs. 22.8a,b, 22.9a,b).

The hairline zone is still constructed with FU (as described above); however, posterior to seven to ten rows of FU, double follicular units (DFU) may be used. If slot grafts or round grafts are employed, they are positioned posterior to the DFU or sometimes posterior to a wider zone of FU instead of a DFU zone. The most posterior aspect of the frontal area is then completed with DFU, FU, or a combination of both. Slot grafts are especially advantageous as they reduce the surface area of the current or future alopecic site and replace it with five to six FU spaced as densely as they were in the donor area. If slot grafts are employed, the second session should ideally occur 5–6 months after the first one in order to fill the spaces between the prior session's slot grafts sufficiently well to avoid graft noticeability. A similar technique is used when round grafts are employed. The final session in the area includes FU scattered between the MUGs to create a background cover of hair in any remaining untransplanted areas. The author primarily uses FU and DFU in all female patients, unless the area to be transplanted is only an extended hairline zone, in which case it is constructed exclusively with FU.

22.3.5.3 Hair Restoration Surgery in the Vertex Area

Hair restoration surgery in the vertex ("crown") area is considerably more demanding than frontal and mid-scalp transplanting. Hair direction and angling are more difficult to mimic if there is existing hair, or to re-create in a natural pattern if there is very little or none present. In addition, the whorl-like direction of hair allows for none of the overlapping or "shingling" of hair that is seen frontally and in the mid-scalp and that creates a denser appearance than occurs without shingling. The author utilizes only FU in the vertex because most patients do not have enough donor reserve to transplant the crown more than once, as well as frontal and mid-scalp areas once or twice each, and FUT is the only type of grafting that looks natural after a single session. Often, a limited area at the center of the whorl can be transplanted a second time, concomitant with transplanting elsewhere, in order to create the appearance of a similar density to

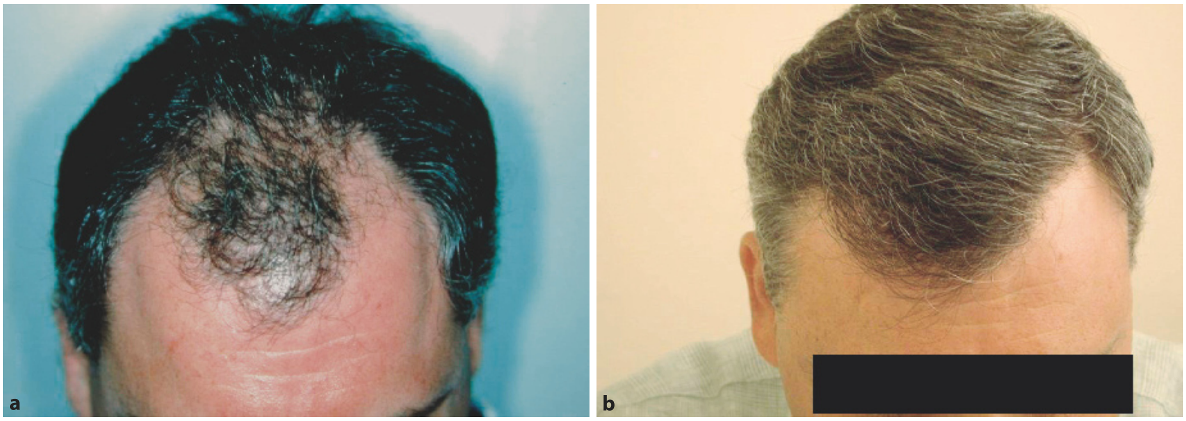


Fig. 22.9 **a** This 54-year-old patient wanted maximum density created in the frontal area. Patient's hair is dyed black. **b** The same patient 9 months after the last of 3½ hair transplant sessions in which a combination of FU, micro-slit grafts, and round grafts of various sizes had been employed. The author believes that extraordinary density cannot be achieved with any other type of grafting. Because it consumes an inordinate amount of donor tissue, it is not suitable for at least 98% of patients that we see. Nevertheless, for those who are suitable and who are prepared to undergo 3 to 3½ sessions, such remarkable results are possible

that seen in the rest of the crown area where there is "shingling" present.

As has been noted previously in this chapter, unless the patient is past middle age and/or has a particularly advantageous family history and physical findings, the author does not generally transplant the vertex until the frontal and mid-scalp areas – and adjacent *future* areas of loss – have been satisfactorily completed *and* he believes a minimum of two sessions are still available from the "permanent" donor area (one for the vertex and one to treat areas of unexpected future loss). Rare exceptions are made for individuals who are more concerned about their vertex loss than their frontal loss, and for those who will be satisfied with reducing the size of the vertex alopecia with peripheral transplanting (Fig. 22.7a,b) if they have sufficient donor tissue for that but not enough for total vertex coverage [40]. All patients are also advised that, because there is little opportunity for overlapping of hair in the crown region, they should be prepared to accept the appearance of a somewhat lower density at that site, than in frontal and mid-scalp areas.

22.3.6 Insertion of Grafts

The increasing use of FUT over the last 5–10 years has resulted in a dramatic increase in the numbers of grafts employed in a typical session, and an increased susceptibility of the follicles within these small grafts (secondary to lethal injury during their preparation, storage, and insertion into the recipient sites). These changes have, in turn, increased the skill, care, and patience required of the assistants, who are an integral and extraordinarily important component of the hair transplant "team." If the assistants are very skilled and dedicated, results are excellent. If, on the other hand, they do not have appropriate hand-eye coordination or are careless the consequence can be reduced graft hair survival. Their skill is especially important during the phase of graft placement. Not only do the grafts need to be kept constantly cool and well hydrated, they should also be handled as little as possible. An excellent technician will grasp the graft with a very light touch – by the subcutaneous "tag" or above the bulb in the wider region of the graft – sense the angle and direction of the incision- and in one motion will slide it into place. Furthermore, the technician needs to control any bleeding, and minimize transmitting pressure on adjacent grafts that have already been positioned in order to avoid "popping." The graft should also sit flat with the surface of the scalp to avoid "delling" (if too deep) or "cobblestoning" (if too high). The assistant needs to concentrate and to be able to see well enough to not miss sites and to discern where the grafts have already been placed, in order to avoid "piggy-backing" one graft on top of another – a situation which can cause the development of an inclusion cyst. While in most offices all the recipient sites are made before any grafts are inserted, the insertion of an FU immediately

after the preparation of each recipient site is generally less traumatic to that graft. Thus, if one is employing FUT with "dense packing," for example 40–70 FU/cm², this "stick and place" method of transplanting is almost certainly advantageous. However, in most offices, "stick and place" is carried out entirely by technicians, leaving them in ultimate control of graft density, as well as the angle and direction of hair growth. Most physicians prefer to leave these parameters in their own hands and hence their preference for incising all the sites first.

22.3.7 Bandaging and Postoperative Care

In our office, for most patients, a turban-like bandage is applied over an initial layer of bacitracin-coated Telfa® pads, and is kept on overnight. It keeps the grafts in place and absorbs any small amount of bleeding that might occur postoperatively. More importantly, every study on wound healing has shown that wounds heal faster and/or better if they are occluded for the first 12–24 h. For comfort, the bandage rests just superior to the ears, but patients are advised to tie a loop of Kerlix gauze over the bandage and under their chin before going to sleep, to prevent accidental slipping of the turban overnight. We remove it the morning after surgery and the hair and scalp are then carefully shampooed. In addition, we check that the grafts have remained in place and make any necessary adjustments. Patients begin washing their hair, on their own, the following day. Soaking of recipient and donor areas for 15 min prior to shampooing, twice daily, is very useful in accelerating the shedding of crusts. During the first week after surgery, patients are also advised to avoid heavy exercise, anything that would cause sweating and/or elevation of blood pressure, and exposure to air that might contain dirt or debris.

A growing number of hair transplant surgeons – especially those employing FUT exclusively – do not use overnight bandaging. We offer a no-bandage option to patients who are having the frontal or mid-scalp areas treated and who do not bleed more than average during surgery. They too return the following day for a "clean-up" and examination of the grafts as described above. A bandage is always employed after vertex transplantation.

The author advocates the application of a 3% solution of minoxidil in an alcohol base just after the recipient area has been cleansed, and twice daily for a period of 5 weeks. It is particularly important to use minoxidil in female patients who seem to be more prone to the *temporary* loss of existing recipient and sometimes adjacent donor area hair. In addition to reducing the likelihood of this temporary postoperative telogen/anagen effluvium, patients have noticed that the effluvium of hair from the transplanted grafts occurs later and the new hair grows back more rapidly as compared to the postoperative course before minoxidil was used.

22.3.8 Postoperative Course and Complications

This subject has been covered in detail in previous publications [33], and includes the following:

- Edema, which occurs in most, though not all, patients beginning usually 1–3 days after surgery and typically lasting for 7–10 days.
- Mild pruritus, which may be treated with a combination corticosteroid-antibiotic cream, for example betamethasone valerate 0.05% in equal parts with gentamicin sulfate cream, applied one to three or more times per day.
- A mild erythematous to violaceous coloring of grafts for a period of 1–3 weeks.
- Occasional slight graft elevation, which can be corrected by simple hyfrecation.
- Rare multi-FU graft depression, which is most easily corrected by excising the graft (which is then used elsewhere in the recipient area) and replacing it with another graft that is properly positioned.
- Hypo- or hyper-aesthesia which results from injured nerves in the donor and/or recipient areas. It lasts for 3–6 months in most patients, but can persist for up to 18 months in a small number of them.
- A permanent small area of hypo-aesthesia occurs in approximately 1% of patients.
- A hematoma, which has been reported but has never occurred in our patients.
- Hypertrophic or keloidal healing scarring which may occur in predisposed individuals. It is extremely rare if patients are screened with an appropriate family and personal history, and examination of prior scars.
- Rare arteriovenous fistulae in either the donor area or (more rarely) the recipient area. They resolve spontaneously over a period of several months. There has been one reported case of this resulting in septic pulmonary emboli [11].

Other potentially serious complications include: (1) infection, which occurs in the donor area in approximately 0.1% of patients and which responds quickly to appropriate topical and systemic antibiotic therapy such as erythromycin 250 mg q.i.d. or dicloxacillin 250 mg q.i.d., (2) osteomyelitis – a single case has been reported in the medical literature [12]; and (3) postoperative

bleeding – virtually zero incidence in the recipient area, and less than 0.1% incidence in the donor area. Usually all that is required to control the bleeding is an additional suture at the site of origin.

To put matters into perspective, all of these complications are very uncommon or rare and mild when the procedure is carried out with skill and care.

22.3.9 Alopecia Reduction

Alopecia reduction (AR) is defined as the excision of an area of alopecia or prospective alopecia. The size of the area that can be excised varies with: (1) the degree of natural scalp laxity, (2) the extent of surgical undermining, and (3) the amount of prior stretching of the hair-bearing rim that creates "biological creep" as a result of scalp "extension" [6] or expansion [17]. The larger the area that can be removed, the smaller the remaining area of alopecia will be, with the result that it can be transplanted using fewer grafts. As has also been discussed earlier, in general, the author recommends that AR be seriously considered any time the objective of the patient is complete and more than light- to moderate-density coverage of frontal, mid-scalp, and vertex alopecia. The more AR procedures that are done, the more likely it becomes that one will not run out of available donor tissue before the entire area of alopecia is treated. Alopecia reduction is also particularly useful for patients who have had prior, cosmetically unsatisfactory, transplanting carried out, and who have very limited donor tissue reserves left to correct problems that may include untransplanted obvious areas. Such areas can be excised instead of transplanted, thus "saving" the grafts that would have been used to do that, for use elsewhere. Despite this obviously advantageous effect, AR of any type has gradually become less and less popular, because of problems related to technical difficulties and unsatisfactory long-term planning experienced by the majority of practitioners. A few experts still produce excellent results but outside of this small group, few hair restoration surgeons employ it. Because of that situation and space limitations, the subject will not be dealt with here. Extensive information is, however, available elsewhere [47].

22.3.10 Flap Surgery

At least four different types of flaps have been extensively used for the correction of alopecia in the past: temporo-parieto-occipital flaps, lateral scalp flaps, long and short temporal vertical flaps, and microsurgical free scalp flaps. The most commonly used flap for MPB is the temporoparietal-occipital or "Juri" flap, but even this design is now only employed by very few practitioners because of technical and long-term planning problems that can be associated with it. Because of space restraints, flap surgery will not be described here. Extensive information is available elsewhere [27].

22.3.11 Cicatricial Alopecia

Patients with cicatricial alopecia may be treated with flap surgery or AR with or without preceding soft tissue expansion. In addition, hair transplanting can be successfully utilized in such individuals [26]. Because the blood supply within the scar is not as good as in normal skin we will often: (1) try to excise as much of the scar as possible prior to utilizing grafting, unless excision has already proved unsuccessful; (2) limit transplanting to FUT; (3) do fewer grafts per session and spread them farther apart than usual; (4) use the smallest gauge needle possible for a given size of FU, to limit vascular injury; and (5) spread sessions farther apart than usual, for example, every 6–12 months. It has become a relatively frequently performed procedure in the author's office primarily for the treatment of patients who have had previous cosmetic surgery in hair-bearing regions and want the resulting scars to be covered with hair. Results have been excellent and there have been no problems with respect to blood supply and growth (Fig. 22.10a,b).

Summary for the Clinician

Since 2000, the techniques for harvesting donor tissue, preparing grafts, and improving hair survival of follicular units have improved dramatically. What we can now expect of hair transplanting has therefore similarly changed in positive and important ways. We have tried to summarize here these changes and their effects. The reader is reminded that different surgeons may employ different routes to achieve very similar results because of the skill that they and their surgical teams have developed with their particular approach. There is no single "best" way in hair transplanting. With improvements in grafting, the need for and use of flaps in hair restoration surgery has decreased but alopecia reduction and particularly scalp extension may yet see a justified resurgence of interest. Most importantly, hair transplantation is now a worthwhile consideration for many more people than was the case as recently as the mid 1990s.

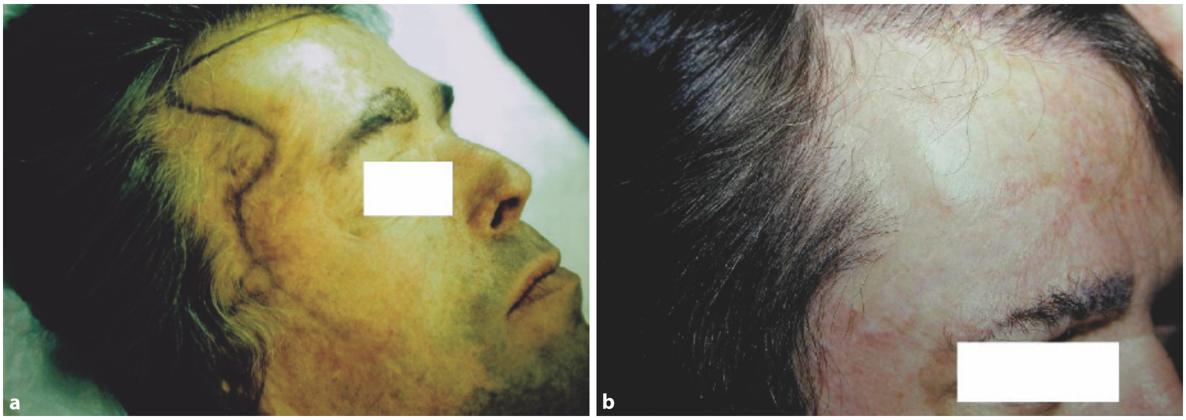


Fig. 22.10 **a** Before transplanting into scarred anterior temporal area subsequent to burn injury in a car crash. **b** After two sessions totaling 1832 FU in the area shown in the photo. Contrary to a widely held belief, cicatricial alopecia, regardless of cause, can be successfully treated with hair transplanting

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Chapter 23

Tropical Dermatoses of the Scalp

Mohsen Soliman, Hiram Larangeira de Almeida Jr.

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23.1 Bacterial Infections of the Scalp

23.1.1 Pyodermas

Synonyms

impetigo contagiosa, epidermal pyoderma, impetigo staphylogenes, impetigo streptogenes

Key Features

- Pyodermal infections of the scalp may be primary or secondary to pruritic conditions; epidermal or adnexial; superficial or deep.
- *Staphylococcus aureus* and Streptococci are the most important causative agents, Gram-negative bacteria are rarely involved.
- Impetigo of the scalp is a frequent complication of pediculosis capitis and seborrheic dermatitis.

23.1.1.1 Introduction

Impetigo contagiosa is the most common superficial primary pyoderma, affecting only the epidermis. It can be caused by *S. aureus* or Streptococci [20]. It may extend to the dermis, when ulcers and crusts are found, in which case the term ecthyma should be used. When bullae (impetigo bullosa) are seen, *S. aureus* is the most probable etiology. The adnexial involvement (folliculitis and furuncles) is also suggestive of *S. aureus* infection. Deeper infections (erysipelas or cellulites) may also occur in the scalp.

23.1.1.2 Epidemiology

Primary infections of the scalp are more common in children in the summer months and may be widespread in class rooms. Secondary infection, also known as impetiginization, of a preexisting dermatosis is seen at any age. Pediculosis capitis, seborrheic dermatitis, poor hygiene, and hot humid weather may be predisposing factors.

23.1.1.3 Clinical Features

23.1.1.3.1 Primary Epidermal Pyodermas

Impetigo contagiosa is characterized by meliceric crusts (honey-crusted sores) (Fig. 23.1) and matting of hair in affected sites, with a relative acute onset. Transient vesicles and pustules at the scalp margin may be seen as well as enlarged tender occipital lymph nodes. In impetigo bullosa large thin-walled blisters with serous yellow fluid or purulent content are seen. In ecthyma ulceration with thick adherent crusting occurs, since the dermis is affected.



Fig. 23.1 Impetigo contagiosa meliceric crusts, erosions and pustules (courtesy of the University of São Paulo)

23.1.1.3.2 Primary Adnexial Pyodermas

Folliculitis is the term for papular or pustular inflammation of hair follicles. A furuncle is a deep-seated inflammatory nodule that occurs around a hair follicle [18], characterized by the development of a conical hard tender red nodule that breaks and becomes fluctuant in a few days, and ruptures discharging pus and a core of necrotic material. A carbuncle is a large inflammatory lesion involving a group of neighboring hair follicles. Localized temporary or permanent hair loss follows the condition.

23.1.1.3.3 Deep Bacterial Infections

Erysipelas represents the infections of dermis with marked dermal lymphatic vessel involvement. Erysipelas is a painful, bright red, raised, edematous, indurated plaque with advancing raised borders, sharply marginated from the surrounding normal skin. Group A beta-hemolytic streptococci are the most common causative organism. Cellulitis is deeper inflammation and extends into the subcutaneous tissues. The tissues feel hard on palpation and are very painful. The hair in the affected areas of the scalp may be shed. Cellulitis may be due to infection with group A beta-hemolytic streptococci, *S. aureus* or *Haemophilus influenzae* in young children [26]. Both are often associated with malaise, fever, and chills.

23.1.1.3.4 Perifolliculitis Capitis Abscedens et Suffodiens (Dissecting Cellulitis of the Scalp)

Perifolliculitis capitis abscedens et suffodiens (dissecting cellulitis of the scalp) (Fig. 23.2) (see Chap 11 for further details) is a chronic form of folliculitis characterized by the presence of multiple nodules and draining abscesses that affect the scalp of young adults. It may be part of the follicular occlusion retention triad that includes acne conglobata, hidradenitis suppurativa, and dissecting cellulitis of the scalp. *S. aureus* secondary infection is common. Healing of older lesions results in hair loss and keloid-like scar. Oral isotretinoin and intralesional triamcinolone acetonide combined with systemic antibiotics will give good control of the case.



Fig. 23.2a,b Multiple abscesses in perifolliculitis capitis abscedens et suffodiens

23.1.1.4 Differential Diagnosis

Inflammatory tinea capitis or Kerion celsi may be confused with scalp pyodermas.

23.1.1.5 Treatment

23.1.1.5.1 Prevention

Hygienic cleansing and daily bath. Check family members for source of organism.

23.1.1.5.2 Topical Treatment

Topical fusidic acid or mupirocin ointments are effective in localized cutaneous lesions when applied three times daily for 7–10 days. Mupirocin could be used to eliminate the organisms from the nares in chronic nasal carriers of *S. aureus* [26] (Table 23.1).

23.1.1.5.3 Systemic Antimicrobial Treatment

It is indicated in disseminated cases of impetigo and in all cases of deep involvement, since topical treatment will not be effective. This depends on culture and sensitivity of isolated organisms, as well on the patient's immunologic condition.

Surgical incision and debridement may be necessary in cases of furuncle or carbuncle.

Table 23.1 Treatment of Pyodermas

Treatment	Level of evidence
Topical mupirocin	1
Topical fusidic acid	1
Oral antibiotics	1

23.1.2 Tuberculosis Cutis

Synonyms
tuberculosis cutis luposa, tuberculosis cutis verrucosa, lupus vulgaris, scrofuloderma

Key Features

- Tuberculosis cutis is an uncommon skin condition with variable presentations and very long clinical course.
- The disease is due to infection with *Mycobacterium tuberculosis*.
- The clinical picture depends upon the immunological state of the patient and the route by which the tubercle bacillus reaches the skin.
- Lupus vulgaris is the commonest, characterized clinically by apple jelly nodules, atrophic scarring and ulceration, of very chronic nature.
- Tuberculous ulcer may be seen. Scalp involvement is rare.

23.1.2.1 Introduction

Tuberculosis is a chronic bacterial infection of the skin that is caused by the human or bovine types of the tubercle bacillus. The attenuated BCG organism (Bacillus Calmette-Guérin) is occasionally the cause of tuberculous disease of the skin. Its incidence used to be in decline (probably due to successful BCG vaccination programs). The recent increase in incidence is often associated with human immunodeficiency virus (HIV) disease. The type of clinical lesion depends on the route of cutaneous inoculation and the immunological state of the host [10]. Cutaneous inoculation results in tuberculous chancre in the non-immune host [24], and tuberculosis verrucosa cutis in the immune host. Endogenous spread to the skin may occur via the bloodstream, as in miliary tuberculosis, or direct extension from an underlying subcutaneous tuberculous process, as in scrofuloderma; in these situations the scalp may be involved.

23.1.2.2 Classification of Cutaneous Tuberculosis

Exogenous infection

- Primary inoculation tuberculosis
- Tuberculosis verrucosa cutis

Endogenous spread

- Lupus vulgaris
- Acute miliary tuberculosis
- Metastatic tuberculous abscess
- Scrofuloderma
- Orificial tuberculosis

23.1.2.3 History

Robert Koch identified the *M. tuberculosis* in lesions of lupus vulgaris in 1882; in 1906 the tuberculin reaction was described.

23.1.2.4 Epidemiology

Primary inoculation tuberculous complex and acute miliary tuberculosis are seen in children. Lupus vulgaris is seen at all ages. Scrofuloderma is seen in adolescents and the elderly. Lupus vulgaris affects females more commonly than males [25]. Dark-skinned people are more affected than Caucasians, with a more unfavorable prognosis.

23.1.2.5 Clinical Features

Various classifications for the disease have been proposed, depending on previous exposure to the tubercle bacillus, mode of infection, and immune state of the patient [10]. The skin is one of the primary sites of *M. tuberculosis* infection.

The characteristic feature of infection occurring in a previously non-infected organism is the so-called primary complex, consisting of a primary tuberculous sore, lymphangitis, and regional lymphadenitis. The host develops an immunological response to *M. tuberculosis* within 3–8 weeks. The tuberculin test becomes positive by that time. Re-infection forms are modified by the host's immune response and route of entry. Inoculation of the organism in persons with moderate to good immunity may give rise to tuberculosis verrucosa cutis. Spreading of the organism from an adjacent or subcutaneous tuberculous process will give rise to scrofuloderma or lupus vulgaris. Hematogenous spread of the organism will give lupus vulgaris, tuberculous gumma or miliary tuberculosis.

23.1.2.5.1 Tuberculous Chancre

The condition has always been a rare event. Tuberculous chancre is the primary inoculation tuberculosis that results from inoculation of the tubercle bacillus into the skin of a patient with no previous exposure to mycobacteria [24]. It is characterized by an ulcerated nodule at the inoculation site. Regional lymph nodes are involved secondarily and complete the tuberculous primary complex. It can persist for weeks to months. Minor trauma on the lower limbs or facial region is the usual predisposing factor. It can also be a complication of BCG vaccination [28].

23.1.2.5.2 Lupus Vulgaris

Lupus vulgaris is the commonest of all forms of tuberculosis of the skin [10, 25]. The lesions are usually solitary and the face is the most commonly affected site, frequently the nose and cheeks; it may present as the classic triad of apple jelly nodules (Fig. 23.3), thin papery scarring, and ulceration. Cases with only ulceration are also seen (Fig. 23.4).

The disease is characterized by its very chronic and destructive nature. The initial lesion is a small tuberculous apple jelly nodule seen on diascopic examination. The nodules are softer than the normal skin. As they increase in size they become slightly protuberant, and



Fig. 23.3 Lupus vulgaris of the scalp, with apple jelly aspect (courtesy of the University of São Paulo)



Fig. 23.4 Ulcerative tuberculosis of the scalp (courtesy of the University of São Paulo)

project above the surface of the skin; but they retain a thin covering of epithelium which presents a smooth and shiny appearance. Peripheral extension is very slow, with the deposition of more and more nodules that tend to coalesce with older ones, forming the lupus patch. Scarring of the central parts of the lesion may give an annular configuration. Scarring is usually atrophic and may be leukodermic. The lesions may extend to cover large areas over decades. Cases of lupus vulgaris may be associated with tuberculous lymphadenitis, lupus of the mucous membranes, tuberculosis of the bones and joints, or pulmonary tuberculosis. The scalp is rarely affected [17, 19, 22], and may be involved in lesions extending from the face, or neck, or in the disseminated form of the disease. Scalp involvement will show scarring alopecia in the middle of the lupus patch. Cases of lupus vulgaris are regularly slowly progressive with no tendency to spontaneous healing. The condition is chronic, extending over years, leading to mutilations and maybe malignant degeneration.

23.1.2.6 Differential Diagnosis

Lupus vulgaris of the scalp should be differentiated from all cases of scarring alopecia. Chronic cutaneous lupus erythematosus, tertiary syphilis, sarcoidosis, lupoid leishmaniasis, deep fungal infections, malignant disease, and lymphoma should be considered. The ulcerative forms may be differentiated from malignant disease and deep fungal infections. Bacteriological and DNA-based tests may be necessary to establish the correct diagnosis.

23.1.2.7 Pathology

Histologically, the lesions will show the classic tubercle with epithelioid cells, Langerhans giant cells, and lymphocytes. Caseation necrosis is seen in 50% of cases. Acid-fast bacilli are seen in 10% of cases. Bacteriological examination and polymerase chain reaction may confirm the suspicion of tuberculosis.

23.1.2.8 Treatment

Prolonged antituberculous therapy with at least two drugs is indicated in all cases: isoniazid (5 mg/kg daily) and rifampicin (600 mg daily), supplemented with ethambutol (25 mg/kg daily), or streptomycin (12.5 mg/kg daily). Isoniazid and rifampicin are given for 9 months, and this can be shortened to 6 months if four drugs are given during the first 2 months (Table 23.2).

Table 23.2 Treatment of lupus vulgaris

Treatment	Level of evidence
Antituberculous therapy	1

23.1.3 Leprosy

Synonyms
hanseniasis, Hansen's disease, Hansen's infection

Key Features

- Leprosy is a chronic granulomatous infection caused by *Mycobacterium leprae* primarily affecting peripheral nerves and secondarily involving the skin and other tissues.
- The extent of the disease is related to the immunologic status of the patient.
- The disease may have high morbidity with mutilations secondary to peripheral nerve lesions.
- Scalp involvement is possible in disseminated forms of the disease.

23.1.3.1 History

Leprosy is cited in the Bible, and in old Egyptian and Chinese works. Leprosy seems to have originated in Eastern Africa or the Near East and then was spread with human migration [16]. To this day it remains a stigmatized condition. Hansen identified the causative agent in Norway in 1874.

23.1.3.2 Introduction

Leprosy is a chronic granulomatous disease, caused by *M. leprae*. It affects principally the peripheral nerves and the skin. Its clinical and histological pictures, course, and prognosis depend on the bacterial load and the immunological response of the patient.

23.1.3.3 Epidemiology

The incidence rate peaks at 10–20 years; and the prevalence peaks at 30–50 years. Males are more often affected than females.

23.1.3.4 Pathogenesis

M. leprae is an obligate intracellular acid-fast bacillus. The organism prefers to grow on cooler parts of the body (e.g., skin, peripheral nerves, testes, upper respiratory tract), and spares warm areas of the skin such as the scalp, axillae, and groin. Droplet infection arises from the oro-nasal mucosa of persons suffering from untreated lepromatous leprosy. The *M. leprae* may occasionally penetrate the skin after trauma (bites, scratches, wounds). The incubation period is usually between 3 and 5 years.

The clinical spectrum, histological pictures, course, and prognosis of leprosy depend on the bacterial load and the immunological response of the patient. The bacteriological load (paucibacillary or multibacillary) will differentiate between its types. The individual cell-mediated immune response (CMI) will determine the form of disease met with [23].

23.1.3.5 Clinical Presentation

There are two major polar types: lepromatous type (LL), with a large number of organisms and poor CMI; and tuberculoid type (TT), with few organisms and a good CMI [13]. Borderline cases [borderline borderline (BB), borderline lepromatous (BL), borderline tuberculous (BT)] and sub-polar types are also recognized. Immunologically mediated inflammatory states (reactional states) may occur spontaneously or after initiation of therapy. They are seen more commonly in the borderline cases.

The scalp is rarely involved in cases of lepromatous leprosy. This may be due to its rich blood supply or its higher temperature, and may occur in advanced lepromatous leprosy cases, with concomitant lesions on the neck or the face.

Lepromatous leprosy may present with macular lepromatous lesions or lepromatous infiltrations (Fig. 23.5) with numerous bacilli in the lesions. The macular lepromatous lesions are diffusely and symmetrically distributed over the body. Nodular lesions or lepromas occur most often in cooler acral parts: ears, brows, nose, chin, elbows, hands, buttocks, or knees. A slow, progressive loss of hair takes place from the outer third of the eyebrows, then the eyelashes, and finally the body; however, the scalp hair usually remains unchanged, characterizing the leonine facies.

The *tuberculoid form* presents with solitary or a few lesions in asymmetrical distribution, and affects the skin and peripheral nerves. The lesions are large, erythematous plaques with a sharply defined and elevated border and flattened atrophic center. The face, limbs, and trunk are common locations for the lesions; the scalp, axillae, groin, and perineum are not involved. The lesions are erythematous, dry scaly, hairless, and anesthetic

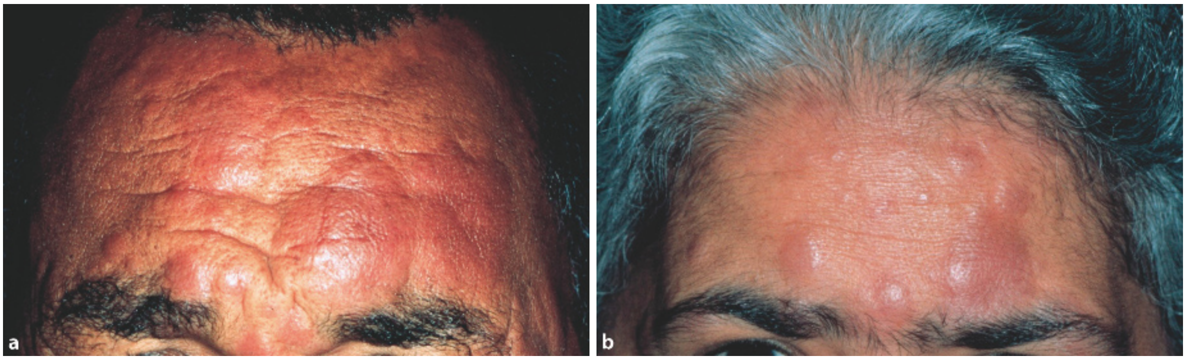


Fig. 23.5a,b Leprosy, typical infiltrative plaques of the lepromatous leprosy (*LL*) form (courtesy of the University of São Paulo)

or hypoesthetic, and anhidrotic. The peripheral nerves serving the lesion are enlarged, tender or both.

Borderline leprosy is the commonest type of leprosy. The borderline tuberculoid leprosy lesions are similar to the tuberculoid lesions, but the lesions are smaller and more numerous. It presents numerous but countable red irregularly shaped plaques, with small satellite lesions surrounding larger ones. In borderline lepromatous leprosy, the lesions are symmetrical, numerous, and may include macules, papules, plaques, and nodules.

23.1.3.6 Differential Diagnosis

Leprosy is differentiated from other lesions showing hypopigmentation or granulomatous lesions, such as lupus vulgaris, syphilis, granuloma annulare, necrobiosis lipoidica or lymphoma. The gold standard for the diagnosis of leprosy is skin histopathological changes.

23.1.3.7 Histopathology

Lepromatous leprosy lesions show an extensive cellular infiltrate that is separated from the flattened epidermis by a narrow Grenz zone of normal collagen. The infiltrate shows abundant macrophages with foamy cytoplasm (Virchow cells) that resemble xanthoma cells. Ziehl–Neelsen stain will show innumerable acid-fast bacilli within the lepra cells, lying in bundles like packs of cigars or, if degenerated, in large clumps called globi [21].

The TL lesions show epithelioid cell granuloma, with occasional giant cells. Lepra bacilli usually are absent from quiescent lesions, and are rarely seen in active or reactional cases.

23.1.3.8 Treatment

The World Health Organization multidrug therapy regimen (Table 23.3) is recommended for all cases of leprosy [13]. The recommendation for paucibacillary disease (no bacilli on smears or biopsy; five lesions or fewer; indeterminate and tuberculoid patients) is 600 mg rifampicin under supervision once a month for 6 months and 100 mg/day of dapsone for 6 months, unsupervised. For single-lesion paucibacillary disease a single dose of 600 mg rifampicin, 400 mg ofloxacin, and 100 mg minocycline, all at one time, is recommended. Multibacillary patients (BT, BB, BL, and LL; more than five lesions; any bacilli seen on smears or biopsy samples) are treated with four drugs: rifampicin 600 mg and clofazimine 300 mg, once a month under supervision, are taken with dapsone 100 mg/day and clofazimine 50 mg/day. Treatment is continued for 12 months. For patients intolerant to clofazimine, the regimen is: rifampicin 600 mg, ofloxacin 400 mg, and minocycline 100mg, all once-monthly for 24 doses (Table 23.3).

Table 23.3 Treatment of leprosy

Treatment	Level of evidence
Multidrug therapy	1

23.1.4 Syphilis

Synonyms
lues

Key Features

- Syphilis is a chronic systemic, sexually transmitted spirochetal infection caused by *Treponema pallidum*.
- If untreated, syphilis passes through the primary stage (chancre) at the site of inoculation to the secondary stage with rash, generalized lymphadenopathy, mucous patches, condyloma latum, alopecia, and other systemic manifestations. Then the disease passes into a latent phase for many years, and then into the tertiary stage with skin, bone, heart or central nervous system involvement.
- The congenital form of the disease is due to prenatal infection of the baby from his or her syphilitic mother.
- Scalp involvement in the secondary stage is not uncommon.

23.1.4.1 Introduction

Syphilis is caused by *T. pallidum* subspecies *pallidum*, an organism seen by dark ground microscopy. Transmission may be by sexual contact or direct (innocent) contact with infectious lesions of early syphilis (chancre, mucous patches, condyloma lata), or blood products. Congenital or perinatal infection may occur [12].

23.1.4.2 History

The causative agent was described by Schaudinn and Hoffmann in 1905 and named *Spirochaeta pallida*. It was recognized in the fifteenth century in Europe and considered a plague. In the United States the incidence of syphilis during the Second World War was around 500,000 infections per year [12].

23.1.4.3 Epidemiology

It can occur at any age: adults, adolescents, and older subjects are affected in decreasing order. All races are affected, and males outnumber females. With the introduction of penicillin and prenatal care the incidence of syphilis diminished [1]. At the start of the acquired immunodeficiency syndrome (AIDS) epidemic, the incidence was low, but a slight increase has been observed recently, to coincide with the introduction of antiretroviral therapy [2].

23.1.4.4 Pathogenesis

The spirocheates pass through the mucous membranes or minor abrasions of the skin to the lymphatics and bloodstream in a few hours. The causative agent divides locally and the inflammatory response results in chancre formation. Cellular immunity results in healing of the primary stage. The disseminated organisms result in the late stages of the disease, with essentially underlying vasculitis.

23.1.4.5 Laboratory Examination

Direct fluorescent antibody *T. pallidum* (DFA-TP) test is used to detect the organism in exudates from lesions, lymph node aspirate, or tissues.

Serologic tests are used after seroconversion of the primary stage, the secondary stage, latent, and late stages of the disease. The serological tests include non-treponemal tests [Venereal Disease Research Laboratory (VDRL) and Rapid Plasma Reagin (RPR) tests] or the treponemal antigen tests [*T. pallidum* immobilization (TPI), *T. pallidum* particle agglutination (TPPA), *T. pallidum* particle hemagglutination (TPHA), and fluorescent treponemal antibody/absorption test (FTA-Abs)].

23.1.4.6 Clinical Features

Primary stage (chancre) usually develops after 9–90 days of exposure to infection [8]. It usually presents as an ulcer that is not painful and is associated with enlargement of the regional lymph nodes. It may be seen on genital areas or on extra-genital locations. Extra-genital lesions are associated with markedly affected lymph nodes. The affected lymph nodes are usually discrete, rubbery, freely mobile, painless, and not attached to the skin or underlying tissues. In this phase dark-field examination is a simple and reliable method for *T. pallidum* demonstration.

Secondary stage is characterized by the appearance of a skin rash that is symmetrical, polymorphic, painless, not itchy, tends to scale slightly, and of coppery red color. The eruption may be macular, papular, pustular or ecthymatous, but not vesicular, showing the pleomorphic characteristic of syphilis; in this phase scalp involvement is not rare (Fig. 23.6).

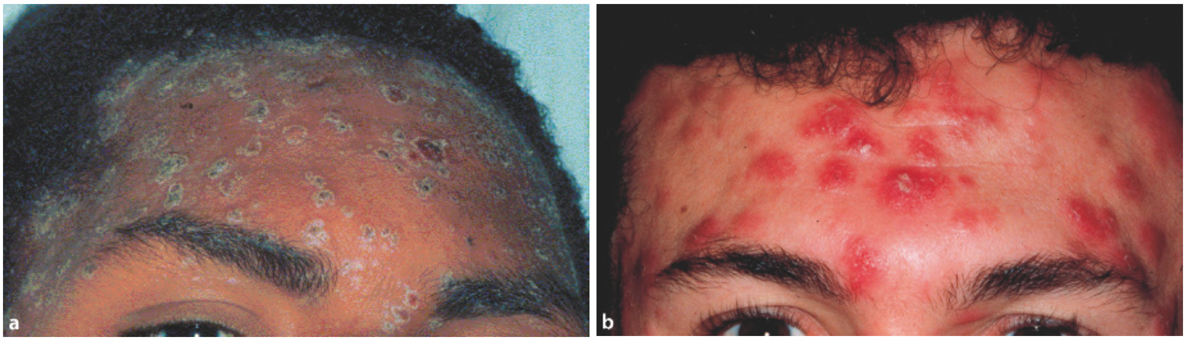


Fig. 23.6a,b Squamous circinate and erythematous papules in secondary syphilis (courtesy of the University of São Paulo)



Fig. 23.7 Syphilitic alopecia (moth-eaten appearance) in secondary stage (courtesy of the University of São Paulo)

Syphilitic alopecia will show scattered, irregular areas of hair loss that have a characteristic moth-eaten appearance (Fig. 23.7). Mucous patches, condyloma lata, generalized lymph node affection, and positive serological tests in all cases are characteristic (VDRL, TPI, TPHA and FTA-Abs).

Latent syphilis may show only positive serological tests.

Tertiary or late syphilis is termed benign when it involves the skin, mucous membranes or bones; and malignant if it involves the cardiovascular or central nervous systems. It will show either gummatous lesions or diffuse syphilitic infiltrations

Congenital syphilis will either show the early congenital manifestations simulating the secondary stage manifestations with bullous lesions and tender osteochondritis, or late congenital lesions known as stigmata; namely, rhagades at mouth corners, saddle nose, Hutchinson's teeth, Parrot' nodes of skull and interstitial keratitis.

23.1.4.7 Treatment

Penicillin remains the drug of choice for treating cases of syphilis. A single shot of 2.4 million units of benzathine penicillin G will usually suffice for treatment of cases of early syphilis (primary and secondary). For patients allergic to penicillin, tetracycline hydrochloride 500 mg 6 hourly or doxycycline 100 mg twice daily for 15 days may be tried (Table 23.4).

Table 23.4 Treatment of syphilis

Treatment	Level of evidence
Benzathine penicillin	1
Procaine penicillin	1
Tetracycline	2
Doxycycline	2

23.1.5 Deep Mycosis and Leishmaniosis

Synonyms
dermal mycosis, subcutaneous mycosis

Key Features

- Cutaneous deep mycosis is characterized by the presence of the causative agent in the dermis, and not in the stratum corneum as in superficial fungal infections. Since the fungi are in contact with blood and lymphatic vessels, extracutaneous and scalp involvement are possible.

Key Features

- The involvement of internal organs may be primary.
- Laboratory investigation is very important to establish the correct diagnosis.
- Leishmaniosis is a protozoal infection with similar features to, and a differential diagnosis of, deep mycosis.

23.1.5.1 Introduction

Deep mycosis can be caused by many agents. Apart from the typical lymphangitis seen in sporotrichosis, there is a wide spectrum of clinical presentations, and diagnosis should be established with laboratorial investigation. Sporotrichosis is a subcutaneous or systemic infection caused by *Sporothrix schenckii*. Paracoccidioidomycosis is caused by *Paracoccidioides brasiliensis. Histoplasma capsulatum* is the etiology of histoplasmosis and *Leishmania* species cause the many forms of leishmaniosis.

23.1.5.2 History

Schenck first reported sporotrichosis in 1898. *Leishmania* were described by Leishman and Donovan in 1903. Adolpho Lutz first described paracoccidioidomycosis in Brazil in 1908 [14].

23.1.5.3 Pathogenesis

The most common route of infection for sporotrichosis is traumatic inoculation, generally when handling vegetables. Scalp involvement is possible in disseminated cases. In paracoccidioidomycosis and histoplasmosis spores are inhaled, leading to a primary complex in the lungs, with possible secondary disseminations to the skin. *Leishmania* species are inoculated by sand flies of the genus *Phlebotomus*, producing a nodular or ulcerative primary lesion, which may evolve to disseminated cutaneous or mucocutaneous forms. Immunologic defenses of the host play a definitive role in the intensity of the disease.

23

23.1.5.4 Clinical Features

Clinical aspects are polymorphous [3, 6, 9, 29] and deep mycosis/leishmaniosis should be suspected in long-standing ulcerations, inflammatory plaques and even pseudo-tumorous lesions (Figs. 23.8, 23.9).





Fig. 23.8 **a** Scalp ulceration in leishmaniosis. **b** Deep infiltrative plaques in paracoccidioidomycosis, leading to secondary alopecia (courtesy of the University of São Paulo)

23.1.5.5 Pathology

A dermal granulomatous reaction with pseudoepitheliomatous hyperplasia may be seen. Fungal elements may be found with silver staining [27], but only *Paracoccidioides brasiliensis* can be identified with light microscopy, with its typical multiple ectospores (pinwheel).

Leishmania can be seen intracellularly with Giemsa staining.

23.1.5.6 Differential Diagnosis

The different forms of deep mycosis should be differentiated from each other, from leishmaniosis, and from mycobacterial infections. Microbiological examination is mandatory to establish the correct diagnosis. DNA-based diagnosis with polymerase chain reaction is a rapid alternative.

23.1.5.7 Treatment

Oral itraconazole is effective in most of dermal mycosis [27]. Intravenous amphotericin B is a hospital-based treatment and an alternative for cases that are resistant or in the severely immunocompromised. The first-line treatments for leishmaniosis are intramuscular antimonials (Table 23.5).

Table 23.5 Treatment of deep mycosis and leishmaniosis

Treatment	Level of evidence
Oral itraconazole	2
Intravenous amphotericin B	2
Antimonials (leishmaniosis)	2



Fig. 23.9 **a** Keloidiform papules in histoplasmosis. **b** Erythemato-squamous plaque with satellite papules in scalp sporotrichosis (courtesy of the University of São Paulo)

23.1.6 Piedras

Key Features

- Piedras are a peculiar group of superficial mycosis, characterized by hard nodular formations that are firmly attached to the hair shafts, which may be dark (black piedra) or white/light-brown (white piedra).
- The word piedra means stone in Spanish.

23.1.6.1 White Piedra

Synonyms
trichosporosis nodosa, piedra alba

23.1.6.1.1 Introduction

White piedra is caused by the yeasts of the genus *Trichosporon* (*T. mucoides*, *T. asahii*, *T. cutaneum*, *T. asteroides*, and *T. inkin*) [11]. It is more common in temperate and semitropical regions, but has been reported worldwide. It may affect not only the scalp, but also the eyebrows, eyelashes, beard, axillary, groin, and pubic hairs. It was also described in monkeys and horses.

23.1.6.1.2 History

Horta distinguished the two subtypes of piedra in 1911 [14].

23.1.6.1.3 Pathogenesis

The mode of infection in human beings is not fully understood; local humidity may be a predisposing factor. The yeasts of the causative genus have been isolated from soil, water, and plant material.

23.1.6.1.4 Clinical Features

The infection is normally asymptomatic. The nodules are visible to the naked eye and often patients note the presence of incrustations on the hairs (Fig. 23.10), leading to a rough sensation of the hair surface.

23.1.6.1.5 Pathology

Scanning electron microscopy shows the elimination of spores on the nodule surface, which has a cheese-like appearance with many canal openings (Fig. 23.11a). Transmission electron microscopy shows hyphae and arthrospores, the same structures as found in culture. Mature hyphae product a cement-like substance, which forms the pseudoparenchyma. Arthrospores have a hairy surface (Fig. 23.11b), which may help to adhere to other hairs during dissemination [4].

23.1.6.1.6 Differential Diagnosis

Black piedra, head lice eggs, and trichobacteriosis may be macroscopically similar to the white piedra nodules. Direct microscopic examination allows differentiation between them. Potassium hydroxide treatment of the concretions shows arthrospores and filaments. If necessary, cultures will show the typical creamy colonies.

23.1.6.1.7 Treatment

Shaving or cutting the affected hairs may be helpful. Topical and systemic azoles were effective in reported cases [4, 11] (Table 23.6).

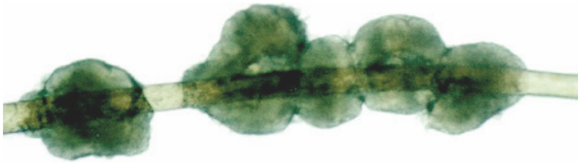


Fig. 23.10 Light microscopy of the typical nodules of white piedra (×200) (reproduced with permission, from [4])

23.1.6.2 Black Piedra

Synonyms
tinea nodosa, trichomycosis nodularis, piedra nigra

23.1.6.2.1 Introduction

Black piedra occurs more frequently in tropical countries in South America, Africa and Asia, affects mainly the hair of the scalp, but also beard and moustache, it has also been described in primates. Among some Indians in the Amazon region it is considered a sign of beauty. The causative agent is the fungus *Piedraia hortai*.

23.1.6.2.2 Pathogenesis

The mode of transmission is not known, but interpersonal contamination is suggested.

23.1.6.2.3 Clinical Features

It is characterized by the presence of firmly adherent black, gritty, hard nodules on the hairs (Fig. 23.12). The affected hair may break as the fungus grows into the hair shaft.

23.1.6.2.4 Pathology

Scanning electron microscopy shows the invasion of the hair keratin by the nodule, and similarly to white piedra the elimination of spores through canals (Fig. 23.13). Transmission electron microscopy shows a complex, well-organized microsystem, in which a pseudoparenchyma with hyphae, arthrospores, and ascospores is identified. The ascospores are secondary to sexual reproduction and are found in thick-walled bags, the asci [5].

Table 23.6 Treatment of white piedra

Treatment	Level of evidence
Oral itraconazole	5
Oral fluconazole	5
Topical azoles	5
Ketoconazole shampoo	5

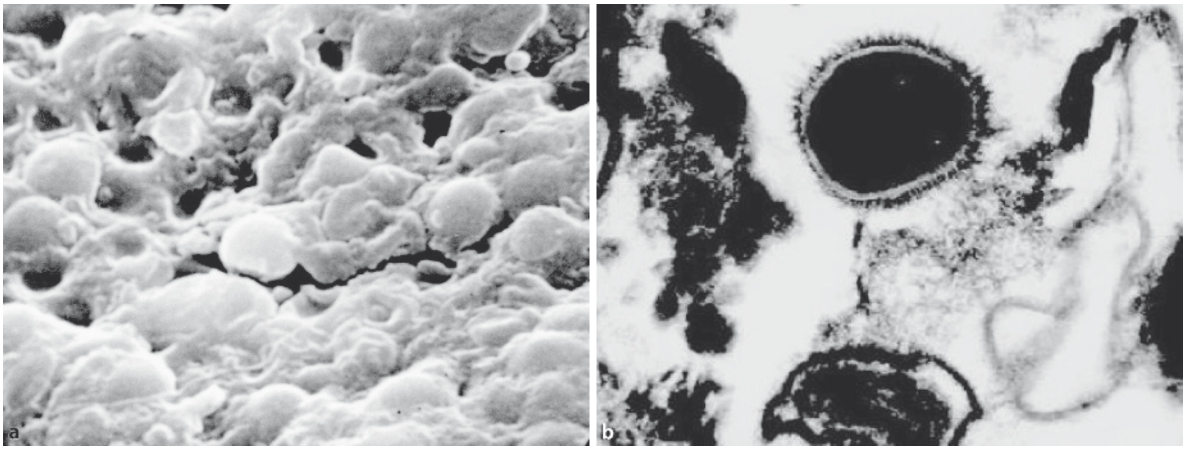


Fig. 23.11a,b Ultrastructural aspects of white piedra. **a** Scanning electron microscopy showing the elimination of spores through canal openings (×3000). **b** Transmission electron microscopy of a spore with a hairy surface (×17,000) (reproduced with permission [4])

23.1.6.2.5 Differential Diagnosis

White piedra and trichobacteriosis may be macroscopically similar. Direct microscopic examination may allow differentiation. Potassium hydroxide treatment of the concretions shows arthrospores and the ascospores, which have a typical aspect of banana-like structures. If necessary cultures will show the typical brown-to-black cerebriform colonies.

23.1.6.2.6 Treatment

Shaving or cutting the affected hairs, if possible. *Piedra hortae* is sensitive to terbinafine and this was successfully when used orally [7] (Table 23.7).

Table 23.7 Treatment of black piedra

Treatment	Level of evidence
Oral terbinafine	5

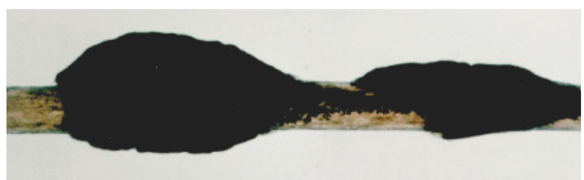


Fig. 23.12 Light microscopy with the dark nodules of black piedra (×70) (reproduced with permission, from [5])

23.2 Nutritional Disorders

23.2.1 Pellagra

Key Features

- Pellagra is one of the nutritional deficiency diseases that may be seen in tropical areas.
- It is due to niacin deficiency and presents with a triad of photosensitivity, diarrhea, and neural and mental disturbances.

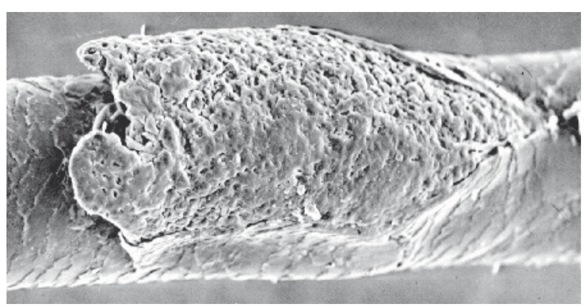


Fig. 23.13 Blackpiedra: Scanning electron microscopy showing a nodule that invades the hair keratin; canal openings are also seen in the surface (×425) (reproduced with permission, from [5])

23.2.1.1 Introduction

Niacin deficiency due to inadequate dietary supply of tryptophan or nicotinic acid is the cause. It is particularly frequent where maize is the main dietary staple, but alcoholism-associated malnutrition and anorexia nervosa can also be found [15]. A high incidence was previously prevalent in Egyptian rural areas where niacin-deficient corn was the source for bread manufacturing, and was replaced by wheat. Administration of isoniazid, which competes chemically with niacin (structural similarity) at its site of action, may provoke a case.

23.2.1.2 Clinical Presentation

The classic triad (3 Ds) of dermatitis, diarrhea, and dementia is rarely seen. Only the skin lesions are seen, diarrhea is less frequently seen, and dementia is rarely encountered. The skin will show redness and scaliness on light-exposed areas and pressure points. It looks like a phototoxic reaction with classic double border at the margin (Fig. 23.14). Typically it affects the butterfly area of the face, front of neck (pellagra necklace), V-shaped area of the upper chest, and dorsa of the hands and feet. The eruption may extend to involve the forehead and scalp. The sunburn-like reaction will leave brown-red discoloration after healing. Diarrhea is rarely an early symptom, and minor depression may be seen.

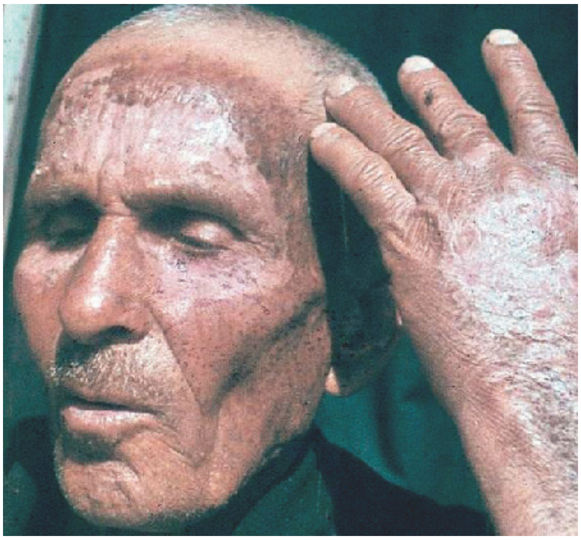


Fig. 23.14 Phototoxic-like reaction, with typical "burned" areas in the frontal region

23.2.1.3 Differential Diagnosis

Hartnup disease will simulate the cutaneous eruption.

23.2.1.4 Treatment

Niacin is given parentally at a dose 50–100 mg daily in severe cases, or 0.5 g orally in mild cases (Fig. 23.14).

Summary for the Clinician

Tropical dermatoses are most often seen in persons living in or returning from tropical areas with its hot and humid climates. This group of diseases comprises certain types of infections that may be endemic in some areas. Other diseases related to environment, climate or socioeconomic factors may occur.

It should be emphasized that easy transportation, the increased mobility of the world's population, traveling voluntarily (tourists, workers, immigrants, and students) or involuntarily (military troops and refugees) has ensured that many of these diseases can occur all over the world and should be considered in the differential diagnosis of scalp lesions.

The scalp has got a unique structure that makes it immune to certain diseases and relatively susceptible to others, however exceptions do occur. Leprosy and tuberculosis are rarely seen on the scalp, probably due to the rich blood supply, or its high temperature compared to other parts of the body, whereas piedra nigra is rarely seen outside the scalp.

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Chapter 24

African Hair

24

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Synonyms

African Hair, African Caribbean hair, African American hair, black hair, negroid hair, ethnic hair

Key Features

For the purpose of this chapter African hair refers to:

- tightly curly black hair
- ellipse or flat on cross-section
- spiral hair follicles by computer-aided three-dimensional reconstruction of biopsy samples
- asymmetric bulb differentiation on immunohistochemistry
- variable fragility with mechanical manipulation.

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24.1 Introduction

The biochemical analysis of hair [13, 39] from people of different geographic origins has proved to be amazingly similar in spite of significant differences in both appearance and behavior (e.g., combability, elasticity), as comprehensively reviewed by Wolfram [61] and Franbourg et al [14]. People of African ancestry, as a group, seem to have a higher prevalence of specific scalp disorders such as dissecting cellulitis and others that may be associated with hair grooming, such as acne keloidalis, traction alopecia, and central centrifugal cicatricial alopecia. The extent to which the curved African hair follicle contributes to the pathogenesis of these conditions remains uncertain.

The United States is likely to be the country with the largest variation in human hair form (phenotype). The African-American population is a heterogeneous group with a mixture of predominantly African, Caucasian, and Native American ancestry. The demographics of the United States are constantly changing and according to the latest U.S. census, it has been projected that in the mid twenty-first century, individuals with dark skin (Africans, African-Americans, Hispanics, and Asians) will be the majority.

Ethnic hair care products are developed specifically to address the needs of African hair. These include an array of products from styling aids to chemical straighteners. Due to the tightly curled hair structure of African hair, sebum from the sebaceous glands is unable to flow down and lubricate the hair shaft adequately. This results in dry brittle hair that is easily broken. Hair pomades or "styling products" are used daily on the hair to correct the breakage and to improve the appearance and manageability. The plethora of hairstyles worn by women and men of African ancestry include chemical and thermal straightening, hair braiding, hair weaving, and natural hairstyles. The clinical significance of hair grooming may contribute to various forms of traumatic alopecia in black women. Understanding cultural hair-grooming practices and the associated ethnic hair and scalp disorders is essential for correct diagnosis and treatment recommendations in this diverse population.

24.2 History

The most significant characteristic of hair morphology is the extent of hair curl. Probably the most exhaustive hair-form study examined eight parameters in hair from seven populations. The results showed participants of Asian ancestry to have the largest diameter and most consistent presence of the medulla. East African hair had the highest kinking, curvature, crimp, and ratio of natural to straight hair [20]. Computer-aided reconstruction of scalp biopsy samples has been used to demonstrate the straight and curly/spiral nature of Asian and African hair follicles, respectively [31]. The findings of this latter study have been confirmed by recent evidence suggesting that it is the asymmetric differentiation of various layers of the bulb that result in the curved hair follicle that is typical of African hair [54].

24.3 Structure and Function/ Pathophysiology/Developments

The unique follicle phenotype is responsible for the different response of African hair to grooming when compared to European and Asian hair, such as more work required to comb the hair [14, 61]. A recent study demonstrated that mechanical fragility of hair increased with higher degrees of curl [44]. Hair removed by combing African hair has been shown to exhibit features consistent with breakage [23], a process equivalent to a daily hair cut, based on the following findings:

- An increase in simple knots, 10%–16% vs. 0.15% compared to other groups.
- Complex knots, intertwining, and partial breaks found only in African hair (Fig. 24.1).
- Less than 40% of African (vs. >80% European and Asian) hair examined presented root sheaths.
- African hair had serrated frayed tips, whereas other groups had cut ends.

The above explains the observation of short hair lengths even after prolonged periods without a hair cut [54]. The short lengths also do not correspond to the widely accepted 1 mm/month growth rate or to the recently reported 0.7 mm/month slower growth rate of African hair [32]. The breakage that occurs with combing increases with dry hair (Fig. 24.2) and is unlikely to be the result of inherent fragility. The sulfur staining of natural African hair is similar to that of Asian and European hair whilst that of patients diagnosed with trichothiodystrophy (TTD) is distinct (Fig. 24.3) [24]. Trichothiodystrophy is a genetic disorder associated with reduced hair sulfur content, the element that gives hair its strength, and is a natural model for hair fragility. The latter studies [23, 24], although consistent with work that suggests asymmetric bulb differentiation [54] and follicle curvature [31] as contributing to the mechanical fragility of African hair, need confirmation in population studies.

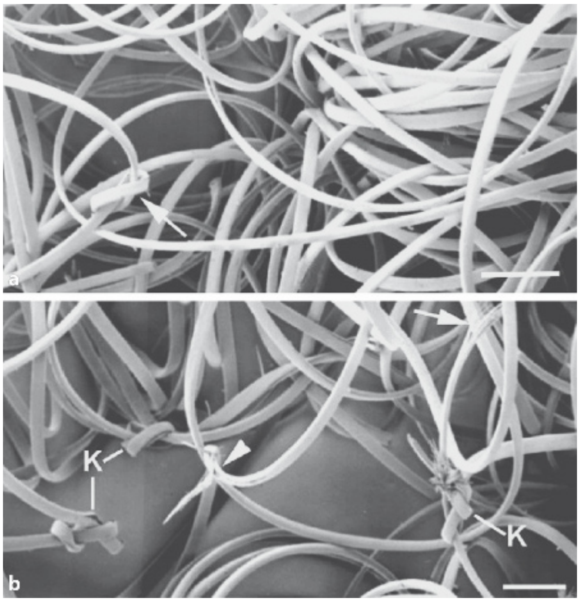


Fig. 24.1 A matt of African hair demonstrating intertwining and knot formation within and between adjacent hairs. (With courtesy of Prof. D.J. Ferguson)



Fig. 24.2 Combing with an "afro" comb – each time the comb is pulled through, the hair springs back forming knots which subsequently become more difficult to comb though; this results in increased broken hair as the hair grows longer, and with dry hair, thus explaining the relatively short hair lengths even after long periods without a hair cut, i.e., a steady state

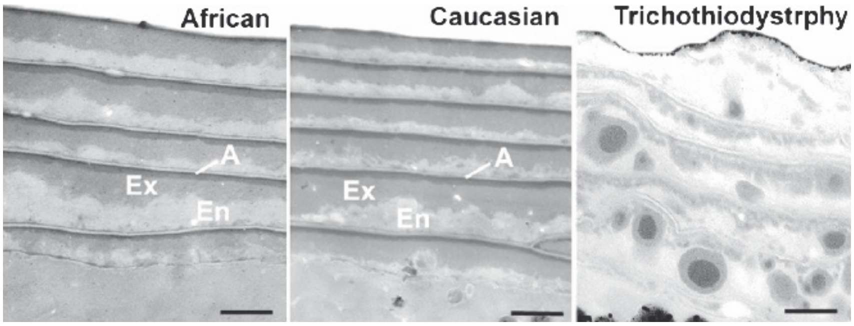


Fig. 24.3 Transmission electron micrographs showing sections through hair cuticles that have been stained with uranyl acetate and lead citrate, illustrating a similar staining pattern with a very electron dense A layer (*A*), electron-dense exocuticle (*Ex*) and electron-lucent endocuticle (*En*) in African and Caucasian hair. Note that the staining in trichorrhexis nodosa shows a disrupted distribution of the cystine-rich proteins with globules of electron-dense A layer and exocuticle-like material. *Bars* are 0.5 µm. (With courtesy of Prof. D. J. Ferguson)

24.4 Experimental Techniques

Methods of investigating the mechanical properties of hair have included in vitro tests using tools such as Miniature Tensile Testers (Dia-Stron, UK) [14, 44, 61], observations using scanning [23, 31] and transmission electron microscopy [24], and immunohistochemistry of scalp biopsy samples, which elucidates various components of the hair follicle [54].

24.5 Clinical Relevance

The phenotype of African hair makes it prone to specific hair and scalp disorders as discussed below. In addition the shape of the African follicle contributes to the tendency for this hair type to be dry, which has to be considered when treating common scalp conditions such as seborrheic dermatitis and psoriasis, which are discussed elsewhere in this book (e.g., Chaps 12, 19). The difficulty



Fig. 24.4 Chemically straightened (relaxed) hair – this is done with caustic chemicals such as sodium hydroxide (lye) and guanidine hydroxide (no lye)



Fig. 24.5 Artistic braids done with artificial extensions in rows (corn rows), traction alopecia is a danger if the style is too tight and left in for too long

associated with combing African hair, politics, culture, and fashion are likely to have contributed to product development for chemical hair straighteners "relaxers" (Fig. 24.4) and grooming preferences such as braids (Fig. 24.5), which are not without undesirable adverse effects [35, 38], although the extent is yet to be quantified.

24.6 Outlook – Future Developments

The discovery of the important role of variable differentiation of the follicular bulb in hair curl opens a potential for its manipulation, genetic and otherwise, to alter hair curl.

Past cosmetic developments have concentrated on altering African hair. It is possible that cosmetic procedures that enhance the natural form of this hair type may be less damaging, as can be seen with virgin hair that is never combed (Figs. 24.6, 24.7). The latter will hopefully not be neglected in future developments. Epidemiological studies are needed to investigate the extent to which factors such as hair follicle anatomy, traction, chemicals, and genetic susceptibility contribute to disease pathogenesis.

24.7 Dissecting Cellulitis

Synonyms
dissecting cellulitis, dissecting folliculitis, perifolliculitis capitis abscedens et suffodiens

Key Features

- Scalp inflammation manifesting with:
- folliculocentric pustules, nodules, abscesses
- later sinuses that burrow, connect or "dissect" under the skin
- eventually permanent or scarring alopecia.
- May be associated with acne and/or other acneiform eruptions.
- Histology reveals a predominantly neutrophilic scarring folliculitis.

24.7.1 Introduction

Dissecting cellulitis (DC) of the scalp is a chronic relapsing inflammatory condition that may be associated with pus-draining lesions, and eventually resolves with permanent hair loss in affected areas. Although it may coexist with other manifestations in distant sites, many patients present with isolated scalp disease.

24.7.2 History

The first report of DC seems to have been in the French literature [16], subsequently the name perifolliculitis capitis abscedens et suffodiens [21] was used. Currently the commonly used name is DC although rarely dissecting folliculitis is also used.



Fig. 24.6 Natural hair that is shampooed and never combed grows longer – hands together with moisturizers and gels can be used to shape the hair



Fig. 24.7 Natural hair that is shampooed and never combed. This style is achieved by separating hair that is a few centimeters long into desired units, which are gently twisted in the same direction after each wash allowing the hair to grow long in these units until it "locks" – a process of irreversible knotting

24.7.3 Epidemiology

There is a lack of published prevalence or incidence data on DC; patients are predominantly men of African ancestry between 20 and 40 years of age, although occasionally other races and women can be affected.

24.7.4 Pathogenesis

Although the mechanism of disease is uncertain, the folliculocentric nature of DC and its usual coexistence with other acneiform disorders suggest that follicular occlusion and subsequent inflammation are contributory factors. The shape of the follicle is likely to be the reason why, unlike acne, DC occurs predominantly in people of African ancestry.

24.7.5 Clinical Features

Early lesions of DC include perifollicular pustules and abscesses; later sinuses and eventual scarring alopecia of the scalp occur. The initial presentation is in adolescence or early twenties. When DC is associated with acne conglobata and hidradenitis suppurativa the syndrome is referred to as the follicular occlusion triad, or tetrad if a pilonidal cyst is also present. The lesions may be painful, ooze pus and become unsightly, which may be distressing to sufferers. Sinus formation is common in established disease and can sometimes be demonstrated by the application of pressure on one lesion resulting in a discharge at a distant site (Fig. 24.8). The latter results because of deep dissecting sinuses that burrow under the skin. The course is chronic and relapsing. Associated musculoskeletal findings are sometimes reported.

24.7.6 Pathology

Dissecting cellulitis is a clinical diagnosis and the histology reveals a predominantly neutrophilic folliculitis with evidence of perifollicular fibrosis and loss of follicles in late disease.



Fig. 24.8 Dissecting cellulitis, deep-seated lesions which burrow under the skin, and occasionally applying pressure at one point results in fluid draining at a distant site

24.7.7 Differential Diagnosis

Very early lesions, particularly if scaly, may be confused with superficial dermatophyte infections. Papules and pustules may mimic folliculitis. Larger pus draining lesions may be confused with ordinary purulent abscesses, particularly because they are often colonized by *Staphylococcus pyogenes* and other pathogens. Cases of the latter mimicking inflammatory fungal infections (kerion) have also been reported [50]. Association (past or present) with other acneiform lesions, if present, may help in the diagnosis of early disease. In addition the chronic and recurrent nature, i.e., limited benefit from standard treatment such as antibiotics, distinguishes DC from all the above conditions. Very rarely, long-standing lesions could be sites of squamous cell carcinomas from chronic irritation [12].

24.7.8 Treatment (Table 24.1)

Long-term antibiotics (3–6 months) and topical steroids can be helpful in very early disease. However, the most effective oral treatment to date has been isotretinoin, but longer courses than those usually used for acne may be required for disease resolution. Unfortunately there have been no controlled trials to substantiate the latter statement but cases of sustained response with long-term follow-up have been reported [47]. Destructive therapies reported include X-ray therapy, electron beam [4, 8], and surgical excision with skin grafting, the largest of which was a report of four patients [59]. Laser epilation of hair follicles is a promising new therapy although more evidence is needed. Common lasers used are the 800-nm pulsed diode laser [4], 694-nm long-pulsed ruby [9], and long-pulsed Nd:YAG (in four patients) [29]. The latter study demonstrated a decrease in drainage and tenderness, partial hair regrowth in 75% of patients and the ability to discontinue systemic therapy. No dyspigmentation was noted at the treatment sites with this longer wavelength laser.

24.8 Acne Keloidalis Nuchae

Synonyms

acne keloidalis (nuchae), dermatitis papillaris capitis, folliculitis keloidalis

Key Features

- Follicular papules and pustules, keloids.
- Usually on nuchal area.
- Males (and females) of African ancestry.
- Permanent scarring.
- Medical treatment may improve early lesions.
- Surgery may be indicated in established disease.

24.8.1 Introduction

Acne keloidalis nuchae (AKN), a scarring alopecia, predominantly affects men of African ancestry and has a predilection for the nuchal scalp, although lesions may be extensive. The lesions may be symptomatic causing unsightly scars which result in permanent hair loss.

24.8.2 History

Acne keloidalis nuchae was first described by Kaposi as dermatitis papillaris capillitii in 1869. Three years later Bazin introduced the term acne keloidalis. Subsequently Fox introduced the less commonly used term folliculitis keloidalis.

24.8.3 Epidemiology

Individual case reports have suggested a predominance of this disorder among African males although there

Table 24.1 Quality of evidence for commonly used treatments

	Antibiotics	Steroids, topical	Retinoids	Other topicals	Surgery/ laser	Cryotherapy IL Steroids	Topical minoxidil
Dissecting cellulitis	5	5	4 Isotretinoin	N/A	4	N/A	N/A
Acne keloidalis	5	3	5 Isotretinoin	N/A	4	3	N/A
Traction alopecia	N/A	N/A	N/A	N/A	5	N/A	5
Central centrifugal cicatricial alopecia	5	5	N/A	N/A	5	N/A	N/A
Pseudo-folliculitis barbae	5	N/A	4 topical retinoids	1 Benzoyl/ peroxide 5%/ clindamycin; 2 Glycolic acid	4	N/A	N/A

Categories: 1 randomized double-blind study, 2 controlled clinical trial >20 subjects, 3 clinical trial ≤20 subjects, 4 case series, 5 anecdotal case reports

have been a few exception, e.g., females and white patients on ciclosporin. A recent systematic review [25] has identified prevalences of 1.3% among patients in a Nigerian skin clinic, 13.6% versus 0% in African and White American football players, and 13.7% among adult male patients in a London skin clinic, although the latter included scalp folliculitis.

24.8.4 Pathogenesis

Although the pathogenesis for this condition has not been worked out, there is some suspicion that hair grooming, particularly very close shaving of skin at the back of the scalp (the so-called fade look) resulting in in-growing hairs, and friction [28] (e.g., the use of caps) may play a role in susceptible individuals. Genetic susceptibility, manifesting as hair follicle shape, is probably pivotal because in the latter study although more white footballers had friction-induced acne mechanica than black players, only the latter presented with AKN in the older group. There is also a possibility that bacteria, especially *S. pyogenes,* found in as much as 95% of affected skin [15] in one report, may be contributory. Sperling et al. suggests that AK is a primary scarring alopecia [53].

24.8.5 Clinical Features

The lesions are predominantly localized to the nuchal scalp in most patients. Although early papules and small keloids predominate in established disease, these may become confluent and form large keloids (Fig. 24.9a). Occasionally multiple papules and small keloids extend toward the vertex (Fig. 24.9b) and even beyond. Although usually asymptomatic, mild itch, irritation, and pain, particularly in the presence of secondary infection, are possible. The overwhelming concern for most patients is the unsightly nature of the lesions.

24.8.6 Pathology

Acne keloidalis nuchae is a clinical diagnosis. However, on histology the most marked inflammation occurs in the infundibulum and isthmus of the hair follicles and is predominantly acute neutrophilic or chronic lympho-



Fig. 24.9a,b Lesions of acne keloid extending toward the vertex and beyond and larger confluent keloids localized to the nucheal scalp

cytic inflammation with occasional granulomas. It is primarily a scarring folliculitis [53] with extensive perifollicular fibrosis in established disease.

24.8.7 Differential Diagnosis

Multiple papules may simulate folliculitis of bacterial or fungal origin and these should be excluded as concurrent disease may occur. Larger confluent keloids may occasionally be secondarily infected and mimic abscesses.

24.8.8 Treatment (Table 24.1)

Oral antibiotics for at least 3–6 months in combination with an antiseptic (povidine) shampoo and topical steroids are often used in early disease. A recent trial has confirmed the benefit of potent topical steroids, and found the foam preparation of clobetasol propionate 0.05% more effective than that of betamethasone valerate 0.12% [7]. Although some benefit with isotretinoin was initially reported the results are not impressive. For established keloids intralesional steroids and cryotherapy are often used in spite of the lack of published evidence in AKN. Extrapolating from the management of other keloids suggests the latter may be helpful. A randomized controlled study of post acne keloid found cryotherapy to be more effective than intralesional steroids [30]. Excision with healing by secondary intention or in combination with radiotherapy, and other destructive procedures such as electron beam therapy and more recently lasers are being tried. More evidence will hopefully become available with time.

24.9 Central Centrifugal Cicatricial Alopecia

Synonyms

CCCA (see Chap 11)

Key Features

- Permanent alopecia in adult females of African origin.
- Asymptomatic gradual thinning of the vertex.

24.9.1 Introduction

Central centrifugal cicatricial alopecia (CCCA) is a devastating form of permanent alopecia that is predominant in females of African ancestry and is suspected of a causal association with hair grooming, although the latter is yet to be proved conclusively.

24.9.2 History

Central centrifugal cicatricial alopecia was originally mistakenly referred to as “hot comb alopecia” [51],

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and later follicular degeneration syndrome (FDS), a name that was abandoned when follicular degeneration of hair follicles was discovered to be an inconsistent finding. A consensus on the histological diagnosis, and that of other scarring alopecia, has recently been published [40].

24.9.3 Epidemiology

The previously mentioned systematic review [25] failed to identify any population studies of CCCA whether in clinical settings or the general public. However, this condition occurs almost exclusively in adult females, although there are rare reports [52] in males of African ancestry.

24.9.4 Pathogenesis

Disease mechanisms have not been elucidated, but the consistent suspicion seems to be an association with hair grooming, whether heat, chemicals or traction. Although the extent to which the shape of the African follicle contributes to pathogenesis is unclear, it is likely to be less important than grooming. The evidence for the latter may be related to CCCA being predominantly a female condition and the differences in styling preference between African males (natural short hair cuts) and females (chemical relaxers, braids, etc.).

24.9.5 Clinical Features

The majority of patients are asymptomatic and complain of thinning of hair on the vertex of the scalp. There are also patients who have a symptomatic episode, burning, and pain soon after the use of chemical relaxers. Whether the latter are cases of early CCCA or chemical burn or contact dermatitis is yet to be elucidated. In early disease examination reveals a widened parting and later more extensive hair loss (Fig. 24.10). The latter is usually without clinical signs of inflammation but with evidence of loss of follicular ostea suggestive of a scarring process (a magnifying lens may make this clearer).

24.9.6 Pathology

Central centrifugal cicatricial alopecia is a clinical diagnosis but biopsy specimens often show end-stage perifollicular fibrosis, earlier lesions may show a lymphocytic inflammatory infiltrate [40], and, as mentioned above, an inconsistent finding of premature follicular degeneration may also be present.



Fig. 24.10 Early central centrifugal cicatricial alopecia presents with a widened central parting; long-standing disease may present with extensive scarring alopecia – evidenced by the loss of follicular ostea

24.9.7 Differential Diagnosis

Burn-out inflammatory scarring alopecia localized in the vertex region (Chaps 11, 12) can, in a person of African descent, be indistinguishable from CCCA. The latter includes conditions such as folliculitis decalvans and pseudopalade. In addition CCCA may occur in a patterned distribution suggestive of androgenetic alopecia and may also coexist with marginal traction alopecia. The latter suggests that traction may also play a role in the pathogenesis of CCCA.

24.9.8 Treatment (Table 24.1)

The most important interventions are early diagnosis and termination of the offending hair style if present. In addition gentle handling of the hair with the use of non-greasy moisturizers and a wide tooth comb, and avoidance or limiting the use of heat, traction, and chemicals should be encouraged. If there is any evidence of inflammation topical steroids and antibiotics may be used initially for 3–6 months, more for their anti-inflammatory than their antibacterial action. In established and severe disease professional advice on wigs and scarves can prove very beneficial. However, weaves and hair pieces that require stitching or gluing on to the hair are best avoided. Hair transplantation has been used anecdotally to surgically treat CCCA after at least 6–9 months of medical therapy with anti-inflammatory agents and biopsy-proven stable disease [6].

24.10 Traction Alopecia

Synonyms
traction alopecia, marginal traction alopecia, traction folliculitis

Key Features

- Short or absent hair usually on scalp margins.
- History of tension-inducing hair style.
- May start with a folliculitis but usually asymptomatic.
- Histology may show increased catagen hair.
- Spontaneous resolution in early disease with hair style change.
- Minoxidil may be helpful in long-standing disease.

24.10.1 Introduction

Traction alopecia (TA) can occur in people of any population and has been described in ballerinas, Sikh men, nurses, Japanese, and Iraqis but most commonly affects African women and children [18, 36] and has been associated with hairstyles [57]. As the name implies, traction in hair styles such as ponytails or braids is thought to induce the condition which if severe can be distressing to affected individuals.

24.10.2 History

The first report of this type of alopecia was by an Austrian dermatologist in nationals of Greenland and he called it “alopecia Groenlandica” [55, 56] as referenced by Hjorth [19]. From the very beginning, hair styles were thought to be the cause of this type of alopecia by such authors as Balina in 1933 as referenced in Slepyan [1, 48]. In 1946 the name traction alopecia was introduced [11].

24.10.3 Epidemiology

People of African decent have dominated published reports and this has been assumed to be related to hair styles. No published general population-based epidemiology studies estimating the prevalence of TA have been identified [25]. A prevalence of 1% has been documented in a London skin clinic and of 33% in a volunteer sample of 110 African women aged between 18 and 35 years [33]. Of concern is the report of TA in children [18]. It will be interesting to see if the prevalence increases in African men among whom cornrows are becoming fashionable.

24.10.4 Pathogenesis

Traction induces an inflammatory folliculitis which may be subclinical, presenting only with progressive alopecia that is initially reversible but may cause permanent hair loss. The exact mechanism of hair loss is still unclear, however the change of terminal hair to small miniature-like hair, particularly at the periphery of lesions of TA, may suggest follicular miniaturization to be the pathogenic mechanism, although this requires further study.

24.10.5 Clinical Features

Some patients have a history of folliculocentric papules and pustules in areas of tension of a hair style or this may be evident in acute presentations. However, the majority have a history of progressive shortening of marginal hair especially on the temples. Eventually the affected scalp becomes smooth but usually there is vellus-like hair evident on the hair line. Hair loss may also be present in other areas of the scalp as dictated by hair styles. Complete resolution in early disease is the rule if tension is avoided, however this is not the case in severe disease (Fig. 24.11).

24.10.6 Pathology

Early lesions of TA are associated with an increased number of catagen and telogen hairs [57]. The end result of traction depends on when the process is interrupted: if early, a complete resolution of the inflammation with hair regrowth occurs. However, prolonged traction results in permanent hair loss which may be associated with evidence of fibrosis and scarring.

24.10.7 Differential Diagnosis

Early papules and pustules may be reminiscent of a bacterial folliculitis but the culture is usually sterile. Depending on the distribution of hair loss, TA may look similar to androgenetic alopecia and early frontal fibrosing alo-



Fig. 24.11 **a** Extensive long-standing traction alopecia – note the short villous-like hairs at the periphery. **b** A patient who kept her hair very short in order to mask her traction alopecia. **c** Evidence of some growth after 3 months on 2% topical minoxidil

pecia. Histological examination will reveal evidence of follicular miniaturization in the latter and scarring alopecia in the former. The possibility of follicular miniaturization in long-standing TA also requires further study.

24.10.8 Treatment

Except for the mention of topical minoxidil use in TA in two unpublished reports [57, 58], a systematic literature search did not reveal a single published report of medical treatments for TA. However, surgical treatment has been described [41]. The evidence for the effectiveness of topical minoxidil was recently reported in an anecdotal study [22] and randomized controlled trials are needed to either confirm or refute the findings; however, medical treatment would be preferable to surgery (Fig. 24.11b, c). The elimination of traction leads to the resolution of the alopecia in most people. An emphasis on education of the public and hair dressers could reduce disease prevalence. It is possible to braid hair without making styles tight, but the belief that tighter braids stay neater for longer, amongst other factors, needs investigation.

24.11 Pseudofolliculitis Barbae

Synonyms
pili incarnati, chronic sycosis barbae, folliculitis barbae traumatica, ingrown hairs, shaving bumps

Key Features

- Chronic inflammatory condition that is caused by sharp ingrown hairs in men and women who shave or tweeze.
- Seen mainly in individuals of African descent with tightly curly hair .
- Women with pseudofolliculitis barbae (PFB) present with unwanted hair on the face (hirsutism), axilla, chest or groin and who shave or pluck (tweeze).
- Etiology is multifactorial including a keratin disorder, K6hf polymorphism, which has been linked to PFB.
- Two mechanisms – extrafollicular and transfollicular penetrance – causing a foreign body inflammatory reaction in the dermis.
- Typical skin lesions consist of follicular papules, pustules, keloids, and hyperpigmentation of the affected areas.
- Treatment is based on shaving recommendations, topical therapy, and laser hair removal.

24.11.1 Introduction

Pseudofolliculitis barbae (PFB) occurs mainly in the beard area of men who shave. It occurs as the result of ingrown hairs that are thick, course and curly, which is common in individuals of African descent. In hirsute women, PFB can occur mainly from tweezing or plucking the facial hair. Involvement also occurs in other areas of hair removal such as the axilla and groin.

24.11.2 History

Pseudofolliculitis barbae was first described by Fox in 1908; Strauss and Kligman referred to this condition as pseudofolliculitis of the beard because of the association with shaving [27]. During the 1960s and 1970s, PFB became a social dilemma in the United States military, when black men were forced to shave in order to adhere to the strict hair grooming requirements of a clean shaven face [3].

24.11.3 Epidemiology

Pseudofolliculitis barbae is an inflammatory condition that occurs in all races, but it mainly affects men of African descent and Hispanics with thick, coarse, curly hair. The incidence varies from 45% to 83% of blacks [17].

24.11.4 Pathogenesis

The etiology of PFB is an inflammatory response manifested as a foreign body reaction surrounding an ingrown hair. This ingrown hair is caused by the curled hair shaft penetrating the epidermis and dermis after shaving. There are two proposed mechanisms of penetration. After shaving, tweezing or plucking the hair, the sharpened hair either re-enters the skin (extrafollicular penetrance) or transects the hair follicle under the skin (transfollicular penetrance), which produces a foreign body reaction within the dermis [5, 17].

Recently, a single-nucleotide polymorphism has been identified that gives rise to a disruptive Ala12Thr substitution in the 1a alpha-helical segment of the companion-layer-specific keratin k6hf of the hair follicle [34, 60]. This genetic marker is partially responsible for the phenotypic expression of PFB in susceptible individuals.

24.11.5 Clinical Features

Pseudofolliculitis barbae produces asymptomatic, painful or pruritic inflammatory papules and pustules in the areas affected (Fig. 24.12a,b). The most common location is the anterior neck in men and the chin in women. Chronic changes include secondary infection (abscesses), postinflammatory hyperpigmentation, atrophic or hypertrophic scars and keloids.

24.11.6 Pathology

The histopathology of PFB involves an invagination of the epidermis produced by the sharp cut end of the hair and a foreign body giant cell reaction within the dermis. Other features include a mixed inflammatory infiltrate with microabscesses, abscess formation within the pseudofollicle, naked hair shafts surrounded by acute and chronic inflammation, and fibrosis.

24.11.7 Differential Diagnosis

Special stains and cultures can help to distinguish between PFB and bacterial or fungal folliculitis. The absence of open and closed comedones helps to distinguish PFB from facial acne vulgaris.

24.11.8 Treatment

Effective control of PFB is achieved by allowing the beard to grow 0.5–1 cm in length. Maintaining this length with electrical clippers that trim the hair to a minimum of 1 mm will help to prevent recurrence [3]. Although cessation of shaving and allowing the hair to grow is often effective, this therapeutic approach is not an option for most women, and for men in some professions a clean shaven face is mandatory. Foil-guarded razors [2] and chemical depilatories, such as barium sulfate or calcium thioglycolates, are alternative hair-removal options.

Medical therapy includes topical corticosteroids, combinations of benzoyl peroxide/clindamycin [10], glycolic acid [42], topical tretinoin [26], and eflornithine hydrochloride [43]. Two of these treatments were described in placebo-controlled trials [10, 42].

Laser therapy is used to target and permanently remove the hair follicle in the treatment of PFB. The laser systems employed include 800–810 nm diode [62], long-pulsed diode [49], long-pulsed 755-nm alexandrite [37], Q-switched Nd:YAG laser with topical carbon suspension [45], and long-pulsed Nd:YAG (1064 nm) [46]. The ruby and alexandrite laser systems may be associated with more side-effects. Lasers emitting wavelengths with high melanin absorption capabilities should be used in a conservative manner when treating patients with dark skin phototypes [37].



Figure 24.12 **a** Pseudofolliculitis barbae in a male patient – follicular papules with hyperpigmentation involving the beard area and neck. **b** Pseudofolliculitis barbae and hyperpigmentation of the chin in a hirsute female patient

Summary for the Clinician

Very curly African hair is associated with specific disorders that may be related to the curly nature of the hair and/or the grooming preferences of people with this hair type. The tendency toward dry and mechanical fragile hair should be considered when treating hair and scalp disorders in people of African ancestry.

Dissecting cellulitis is a chronic relapsing inflammatory condition of the scalp. Early diagnosis and treatment with long-term antibiotics and topical steroids may be useful but isotretinoin is the most effective treatment that prevents permanent scarring. Surgery may be indicated in long-standing disease.

Acne keloidalis nuchae is a chronic inflammatory condition usually in the nuchal scalp of men of African ancestry who have frequent short cuts. Removing causal factors, if present, is the initial step in management. In addition long-term antibiotics, potent topical steroids for early disease, and surgery may be indicated in long-standing disease. Early treatment will prevent unsightly permanent scarring.

Central centrifugal cicatricial alopecia is a condition that remains an enigma. Except for the clinical picture of scarring alopecia, which spreads out from the vertex of the scalp of females of African ancestry, and the suspicion of an association with hair grooming little else is known. Until future evidence becomes available, early diagnosis, prevention of further damage and symptomatic treatment, where indicated, are the mainstay of management. In severe disease information on wigs and prosthesis is helpful.

Traction alopecia is usually asymptomatic but when severe can result in emotional problems. The most important thing is to avoid tight hair styles and in some patients it may be necessary to stop braids altogether. Topical minoxidil 2% and hair transplantation may be helpful in long-standing disease but randomized trials are needed to confirm the benefit.

Pseudofolliculitis barbae is a common inflammatory skin problem in black men and women who shave or tweeze and often leads to postinflammatory hyperpigmentation. The etiology of PFB involves an intense foreign body reaction in the skin as a result of an ingrown curly hair. Treatment options include cessation of shaving or tweezing and allowing the hair to grow 0.5–1 cm in length, chemical depilatories, topical and oral antibiotics, topical corticosteroids, topical retinoids, topical eflornithine, and laser therapy. Combination therapy is the most effective.

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Chapter 25

Hair Cosmetics

Zoe Diana Draelos

25

Synonyms

hair shampoos, hair conditioners, hair styling aids, hair dyes, hair permanent waving, hair straightening

Key Features

- Hair shampoos are composed of synthetic detergents designed to remove sebum and environmental dirt from each individual hair shaft without decreasing the cosmetic appearance of the hair.
- Hair conditioners are designed to improve hair manageability, decrease hair static electricity, add luster, prevent UV-induced photodamage, and enhance styling ease.
- Hair styling aids are intended to maintain the hair in a fashionable arrangement while improving the quality of the hair fibers.
- Hair dyes can lighten or darken an existing hair color while covering canities in a temporary, semipermanent, or permanent manner.
- Permanent hair waving repositions hair keratin disulfide bonds in a new curly conformation while hair straightening repositions hair keratin disulfide bonds in a new straight position.

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25.1 Introduction

Hair cosmetics are designed to both maintain the hygiene of the scalp and adorn the head. For example, shampoos must clean the scalp to prevent infection while hair conditioners are intended to beautify the freshly washed hair. However, there are some hair cosmetics utilized simply to alter the hair in a fashionable style. These hair cosmetics include hair styling agents, dyes, and permanent waves. This chapter presents the relevant chemistry of each of these products while highlighting key dermatologic issues.

25.2 Shampoos

Shampoo is a cleanser designed to remove sebum, eccrine sweat, apocrine sweat, fungal elements, desquamated corneocytes, styling products, and environmental dirt from the scalp and hair [39]. The main purpose for a shampoo is to cleanse the scalp, but most patients would disagree stating that the purpose of shampoo is to beautify the hair. This perception that a shampoo can impart cosmetic value to nonliving hair shafts has led to the tremendous plethora of shampoos on the market today [55]. This section delves into the formulation, efficacy, and variety of liquid mass-market shampoos.

25.2.1 History

Cleansing the hair is actually a complex task, since the average woman has 4–8 m^2 of hair surface area to clean [3]. It is very easy to formulate a shampoo that will remove dirt, but hair that has had all the sebum removed is dull in appearance, coarse to the touch, subject to static electricity, and more difficult to style [28]. Traditional bar soaps are not recommended for hair cleansing because they leave behind a soap scum when mixed with hard water that is difficult to rinse from the hair and scalp. This may be one of the aggravating factors for seborrheic dermatitis. Table 25.1 lists the general ingredient categories and their function in a basic shampoo formulation [16].

25.2.2 Technology

Shampoos function by employing detergents, also known as surfactants, which are amphiphilic. This means that the detergent molecule possesses both lipophilic, or oil-attracting, and hydrophilic, or water-attracting, sites. The lipophilic site binds to sebum and oil-soluble dirt while the hydrophilic site binds to water allowing removal of the sebum with water rinsing [65]. Typically, several detergents are combined together to achieve the desired end result [42]. For example, if the shampoo is intended for oily hair, detergents with strong sebum-removal qualities are selected, conversely if the shampoo is intended for permanently waved or dyed hair, mild detergents are selected to reduce sebum removal. The art of shampoo formulation is selecting the right detergent combination to cleanse the scalp and beautify the hair simultaneously. The most commonly used shampoo detergents are listed in Table 25.2.

There are four basic categories of shampoo detergents: anionics, cationics, amphoterics, and nonionics (Table 25.3) [50]. Each of these groups possesses different hair cleansing and conditioning qualities, which are combined to yield the final shampoo characteristics. Anionic detergents are the most popular surfactants used in basic cleansing shampoos in the current market. They are named for their negatively charged hydrophilic polar group. Anionic detergents are derived from fatty alcohols and are exceptionally adept at removing sebum from the scalp and hair. Unfortunately, the aesthetics of thoroughly cleaned hair are not well accepted by the consumer. Hair devoid of all sebum is harsh, rough, subject to static electricity, dull, and difficult to detangle. There are several common detergents categorized within the anionic group: ammonium lauryl sulfate, ammonium laureth sulfate, lauryl sarcosine, and disodium oleamine sulfosuccinate.

25.2.3 Anionic Detergents

The anionic detergents previously discussed are named for their negatively charged polar group, while the cationic detergents are named for their positively charged polar group. The cationic detergents are not nearly as popular in current shampoos as the anionic detergents

Table 25.1 Basic shampoo ingredient formulation and function

Detergents	Functions to remove environment dirt, styling products, sebum, and skin scale from the hair and scalp
Foaming agents	This agent allows the shampoo to form suds, since consumers equate cleansing with foaming even though the two are unrelated
Conditioners	Leave the hair soft and smooth after sebum removal by the detergent
Thickeners	Thicken the shampoo, since consumers feel that a thick shampoo works better than a thin shampoo
Opacifiers	Added to make a shampoo opaque as opposed to translucent for aesthetic purposes unrelated to cleansing
Sequestering agents	Function to prevent soap scum from forming on the hair and scalp in the presence of hard water; the basic difference between a liquid shampoo and a bar cleanser
Fragrances	Added to give the shampoo a consumer-acceptable smell
Preservatives	Prevent microbial and fungal contamination of the shampoo before and after opening
Specialty additives	Treatment ingredients or marketing aids added to impart other benefits to the shampoo besides hair and scalp cleansing

Table 25.2 The most common shampoo detergents

1. Sodium laureth sulfate
2. Sodium lauryl sulfate
3. TEA lauryl sulfate
4. Ammonium laureth sulfate
5. Ammonium lauryl sulfate
6. DEA lauryl sulfate
7. Sodium olefin sulfonate

Table 25.3 Shampoo detergent characteristics

Surfactant type	Chemical class	Characteristics
Anionics	Lauryl sulfates, laureth sulfates, sarcosines, sulfosuccinates	Deep cleansing, may leave hair harsh
Cationics	Long chain amino esters, ammonioesters	Poor cleansing, poor lather, impart softness and manageability
Nonionics	Polyoxyethylene fatty alcohols, polyoxyethylene sorbitol esters, alkanolamides	Mildest cleansing, impart manageability
Amphoterics	Betaines, sultaines, imidazolinium derivatives	Nonirritating to eyes, mild cleansing, impart manageability

because they are limited in their ability to remove sebum and do not produced the abundant lather desired by consumers. In addition, cationic detergents cannot be combined with anionic detergents, limiting their utility. Cationic detergents are primarily used in shampoos where minimal cleansing is desired, such as in daily shampoos designed for permanently dyed or chemically bleached hair. Cationic detergents are excellent at imparting softness and manageability to chemically damaged hair [3].

25.2.4 Nonionic Detergents

The nonionic detergents are the second most popular surfactant, behind the anionic detergents. They are named nonionic since they have no polar group. These detergents are the mildest of all surfactants and are used in combination with ionic surfactants as a secondary cleanser [36]. Examples of commonly used nonionic detergents include polyoxyethylene fatty alcohols, polyoxyethylene sorbitol esters, and alkanolamides.

25.2.5 Amphoteric Detergents

The term amphoteric refers to substances that have both a negatively charged and a positively charged polar group. Thus, amphoteric detergents contain both an anionic and a cationic group, which allows them to behave as cationic detergents at lower pH values and as anionic detergents at higher pH values. These properties make amphoteric detergents quite unique. Within the amphoteric detergent category, there are several subgroups that include the betaines, sultaines, and imidazolinium derivatives. Amphoteric detergents, such as cocamidopropyl betaine and sodium lauraminopropionate, are found in baby shampoos. These detergents actually numb the tissues of the eyes accounting for the nonstinging characteristics of baby shampoo. Amphoteric detergents are also used in shampoos for fine and chemically treated hair because they foam moderately well while leaving the hair manageable.

25.3 Conditioners

The need for hair conditioners arose following technological developments in detergents and shampoo formulation. Originally, bar soaps were used to clean both the hair and the body. Most bar soaps possessed an alkaline pH, which swelled the hair shaft leaving it unattractive and unmanageable. In addition, most homes used well water for cleansing with a high mineral content. The combination of the bar soap and hard water yielded soap scum that accumulated on the tub and also on the hair. This soap scum left the hair harsh and dull adding an additional source of scalp irritation.

The widespread use of municipal water sources and the development of liquid synthetic detergents that were formulated at a neutral pH with sequestering agents revolutionized hair shampooing. Now the shampoos left the hair soft and manageable and could be used more frequently without an adverse cosmetic result. This led to the current practice of shampooing daily or every other day, which efficiently removes sebum from the hair shaft [19]. Sebum is, of course, the ideal hair conditioner. Excessive removal of sebum created the need for a synthetic sebum-like substance able to minimize static electricity, increase hair shine, improve hair manageability, and also aid in maintaining a hair style. Thus, hair conditioners were developed in an attempt to supply hair with the positive attributes of sebum while avoiding the greasy appearance indicative of excessive sebum and dirty hair.

Conditioners are liquids, creams, pastes, or gels that mimic sebum in making the hair manageable, glossy, and soft. The role of conditioners goes beyond maintaining the appearance of healthy hair. Conditioners also attempt to recondition hair that has been damaged by chemical or mechanical trauma [47]. Common sources of trauma include excessive brushing, hot blow-drying, permanent hair waves, hair straightening, and hair bleaching. Damage to the hair shaft can also occur through environmental factors such as exposure to sunlight, air pollution, wind, seawater, and chlorinated swimming pool water [64]. This type of hair damage is technically known as "weathering" [40]. Obviously, since hair is nonliving tissue, any reconditioning that occurs is minimal and temporary until the next shampooing.

25.3.1 History

Hair conditioners were developed during the early 1930s when self-emulsifying waxes became available. These waxes were combined with protein hydrolysates, polyunsaturates, and silicones to give the hair improved feel and texture. Early sources of protein included gelatin, milk, and egg protein [15]. Currently, the most common ingredient in hair conditioners is silicone. Silicone is a lightweight oil that can leave a thin film on the hair shaft without creating the appearance of dirty hair. The amount of silicone left behind on the hair shaft determines whether the product is designed for adding body to fine hair where minimal conditioning is desirable or straightening curly hair where maximal conditioning is desirable.

25.3.2 Technology

There are several different active agents that can be combined to achieve a hair conditioner designed for a given hair type. The more common conditioner ingredients are presented in Table 25.4 [10]. Hair conditioners are also available in several types, depending on their intended function and when in the grooming process they are applied [4, 17, 26]. The major types of hair conditioners are summarized in Table 25.5.

25.4 Styling Aids

Hairstyles are in part dictated by the available technology in hair styling products.

The role of the physician is to understand how these products impact the hair and skin [30]. This section discusses the formulation and use of hair sprays, gels, waxes, mousses, pomades, brilliantines, oil sheen sprays, and curl activators (Table 25.6).

25.4.1 Technology

25.4.1.1 Spray

Hair spray is an aerosolized liquid applied to the hair following styling to maintain the hair in the desired position [21, 24]. Hair sprays employ copolymers, such as polyvinylpyrrolidone (PVP), which add stiffness to the individual hairs and create temporary bonds between the hair shafts. Polyvinylpyrrolidone is a resin that is soluble in water and easily removed by shampooing; however, it is also able to absorb water. This means that the hair spray film will become sticky when mixed with perspiration, humidity, or precipitation. Also, the hair will no longer maintain the desired style. In order to make high-hold hair sprays, the PVP was mixed with vinyl acetate (VA) to form a new polymer (PVP/MA). While VA made the hair spray more resistant to water in the environment, it also made the hair spray harder to remove with shampooing [54]. This led to the development of other copolymer resins of vinylmethylether and maleic acid hemi-esters (PVP/MA) and copolymer

Table 25.4 Common hair conditioners

Hair conditioner category	Primary ingredient	Main advantage	Hair grooming benefit
Cationic detergent	Quaternary ammonium compounds	Smooth cuticle, decrease static electricity	Excellent to restore damaged, chemically processed hair
Film former	Polymers	Fill hair shaft defects, decrease static electricity, improve shine	Improve the appearance of dry hair, improve grooming of coarse, kinky hair
Protein-containing	Hydrolyzed proteins	Penetrate hair shaft to minimally increase strength	Temporarily mend split ends
Silicones	Dimethicone, cyclomethicone, amodimethicone	Thin coating placed on hair shafts	Decrease static electricity, decrease combing friction, add shine

Table 25.5 Hair conditioner product type

Type	Use	Indication
Instant	Apply following shampoo, rinse	Minimally damaged hair, aids wet combing
Deep	Apply 20–30 min, shampoo, rinse	Chemically damaged hair
Leave-in	Apply to towel-dried hair, style	Prevent hair dryer damage, aid in combing and styling
Rinse	Apply following shampoo, rinse	Aid in disentangling if creamy rinse, remove soap residue if clear rinse

Table 25.6 Hair grooming cosmetics

Styling product	Formulation	Application
Hair spray	Aerosolized spray polymer	Sprayed on a finished hair style
Hair styling gel	Clear gel polymer	Rubbed with the hands onto towel-dried hair
Hair sculpturing gel	Clear gel higher concentration polymer	Rubbed with the hands onto towel-dried hair
Hair wax	Soft opaque formable wax	Massaged into dry hair shafts after softening in the palm
Hair mousse	Aerosolized polymer foam	Squirted onto the hand and dabbed through towel-dried hair
Pomade	Ointment of petrolatum	Combed with the hands through washed or unwashed hair
Brilliantine	Liquid oil	Massaged with the hands through washed or unwashed hair
Oil sheen spray	Aerosolized oil	Sprayed onto washed or unwashed hair
Curl activiator	Clear glycerin gel	Massaged with the hands through washed or unwashed hair

resins of VA and crotonic acid or dimethylhydantoin-formaldehyde [34]. The newest flexible-hold hair sprays that provide high hold with reduced stiffness may contain methacrylate copolymers, such as polyvinylpyrrolidone dimethylaminoethyl methacrylate (PVP/DMAEMA) [46, 63].

25.4.1.2 Gel

Hair gels are similar to hair sprays, except that they are squeezed from a tube rather than sprayed from a bottle. This product is applied to towel-dried, damp hair, and distributed on the hair shafts by hand combing to form a thin film. If a small amount of gel is applied, the hair will have a natural look and feel. If a large amount is applied, the hair will have a wet, “spiky” look and a stiff feel. Hair gels contain the same PVP-type copolymers as hair sprays and offer enhanced hold, increased hair shine, and some conditioning [59]. Hair gels are available in two types: styling gels and sculpturing gels. Styling gels offer moderate hold while sculpturing gels offer strong hold allowing the creation of gravity-defying hair styles. This is particularly important in persons with thinning hair, since the eye interprets hair thickness by the hair elevation over the crown and the lateral displacement at the sides of the head [9]. Hair gels can hold the hair away from the scalp, creating the illusion of fullness [41].

25.4.1.3 Wax

Hair waxes are relatively new products designed to add increased hold to hair. They too rely on polymers, but the polymers are designed to soften at body temperature. Also, the polymers can be easily re-formed, providing a styling product that can be reshaped frequently yet allow the hair to remain in position. These are the products that allow the “bed head” look where the hair stands straight on end away from the scalp, but has a rather greasy appearance. These products are scooped from a can by the fingers and allowed to soften in the palm prior to application. They are massaged along the length of the hair shafts to provide an even, thin coating. Hair waxes are popular among young persons with very short hair.

25.4.1.4 Mousse

Hair mousses are unique styling products in that they are released as foam from an aerosolized can. The mousse is applied in the same manner as a hair gel to towel-dried hair. It can also be applied to dry hair to create a wet, “spiky” look. Hair mousse yields a lighter copolymer application and does not provide as strong a hold as gel formulations. It also produces less flaking and stickiness under moist conditions. Men generally prefer this product.

25.4.1.5 Pomade

Hair pomades are designed to straighten, condition, moisturize, and add shine to kinky hair found in African-American persons. Pomades, also known as cream brilliantines, are anhydrous products containing petrolatum, waxes, lanolin, and vegetable or mineral oils [20]. Treatment pomades may also contain sulfur, vitamins, or tar derivatives to minimize the recurrence and symptoms of dandruff or seborrheic dermatitis. The thick pomade ointment helps minimize combing friction in tightly kinked hair preventing hair breakage with styling through lubrication. The petrolatum also prevents water evaporation, a common unwanted side-effect of hair straightening. The pomade can also act as a styling product to allow the hair to remain close to the scalp with some curl reduction.

25.4.1.6 Brilliantine

Pomades are ointments while hair brilliantines are liquids. Liquid brilliantines are popular for maintaining natural, kinky hairstyles. These products allow ease of styling and provide shine without causing an oil build up. Traditionally they contain mineral and vegetable oils and may be comedogenic [1, 37]. Newer formulations contain silicone to add lubricity, castor oil to aid in manageability, and soluble glycoprotein to maintain proper moisture balance and enhance shine [53].

25.4.1.7 Oil Sheen Spray

Hair sprays for kinky hair must contain a high concentration of conditioners. One unique form of hair spray for African-American hair is the oil sheen spray. This is an aerosolized oil, for example containing mineral oil and silicone, which is sprayed onto the hair on a daily basis to moisturize and decrease combing friction. It may also contain steartrimonium hydrolyzed animal protein and a difatty cationic amino acid derivative for additional shine and moisturization.

25.4.1.8 Gel Curl Activator

The previously discussed pomades, brilliantines, and oil sheen sprays are designed for straightened or relaxed hair; however, these products are not suitable for use on kinky hair that has undergone permanent waving to create soft ringlets. The permanent waving of African-American hair to create soft curls is known as a "Jheri Curl," after the name of the company that popularized the hairstyle. This hairstyle requires moisturization, but the heavy ointments and oils would prevent the curls from forming. Gel curl activators were developed specifically for this ringlet hairstyle. They are based on glycerin, which functions as a humectant to attract water to the hair shafts. These clear gels are scooped from a jar and stroked through the hair prior to styling, but do not moisturize quite as well as the traditional pomades. Recently, they have fallen out of popularity because glycerin leaves the hair sticky and also attracts dirt requiring frequent shampooing. Unfortunately, the glycerin also was not water resistant meaning that the entire hair style had to be redesigned with each shampooing.

25.5 Dyeing

Hair coloring is a technique used by both men and women for altering the natural hair color or camouflaging the presence of gray hair [7]. The hair color can be changed until the next shampooing, for 8–12 shampooings, or permanently [13]. It can be dyed darker than the original hair color or lightened. This invention has added a new dimension to hair cosmetics and created a huge at-home hair dye and salon industry.

25.5.1 History

Even though henna and indigo have been used to color hair for over 3000 years, modern synthetic organic chemistry has made the twentieth century the era of hair color. The whole hair coloring industry began when Hoffman in 1863 noticed that paraphenylenediamine produced a brown-black coloration when oxidized. But, the transfer of knowledge was slow in the late 1800s and it was not until 1907 that Eugene Schueller marketed the first commercial brand of hair color in 1907. He was a chemist and the founder of L'Oréal, still a leader in hair coloring technology today. Originally, hair coloring was limited to the professional salon, but in 1950 the first home-use hair dye was introduced.

25.5.2 Technology

The principle use for hair dyeing is to cover gray hair. The mechanism of graying is not totally understood, however. It is thought that the death of some melanocytes within the hair-melanocyte unit triggers a chain reaction resulting in the death of the rest of the unit's melanocytes in a relatively short period [8]. A possible

mechanism of death is the accumulation of a toxic intermediate metabolite, such as dopaquinone [52].

Several different hair dye cosmetics have been developed: gradual, temporary, semipermanent, and permanent. Approximately 65% of the hair dye market purchases are for permanent hair colorings, 20% for semipermanent colorings, and 15% for the remaining types. Each type will be discussed in detail (Table 25.7).

25.5.3 Gradual

Gradual hair dyes, also known as metallic or progressive hair dyes, require repeated application to result in gradual darkening of the hair shaft. This product will change the hair color from gray to yellow-brown to black over a period of weeks [35]. There is no control over the final color of the hair, only the depth of color, and lightening is not possible. They employ water-soluble metal salts which are deposited on the hair shaft in the form of oxides, suboxides, and sulfides. The most common metal used is lead, but silver, copper, bismuth, nickel, iron, manganese, and cobalt have also been used. In the United States, 2%–3% solutions of lead acetate or nitrate are used to dye the hair while 1%–2% solutions of silver nitrate are used to dye eyelashes and eyebrows [44].

The popularity of gradual hair dyes is due to their low cost and the ability to perform the dyeing procedures at home without the assistance of a professional operator. They must be properly applied, however, or poor color quality stiff, brittle, and dull hair may result. In addition, the trace metals left on the hair do not allow predictable results when combined with other dyeing or permanent waving procedures. The metal can cause breakdown of

Table 25.7 Types of hair dye

Hair dye type	Chemical reaction	Anticipated end result	Duration of effect	Advantages	Disadvantages
Gradual	Deposition of metal salts	Gradual brown hair darkening	Requires continuous application	Inexpensive, easy to apply	Cannot be combined with other chemical hair processing
Temporary	Acid textile dyes	Blending of hair tones	One shampoo exposure	Short-lived, inexpensive	May rub off on clothing or run with water exposure
Semi-permanent vegetable	Henna with metal salts	Reddish hues to hair	Four to six shampoo exposures	Low incidence of allergenicity	Leave hair somewhat harsh
Semi-permanent textile	Textile dyes	Tone hair, minimally cover gray	Four to six shampoo exposures	Add color highlights	Short-lived color
Semi-permanent	Deeper penetrating textile dyes	Tone hair, minimally cover gray	Ten to twelve shampoo exposures	Longer lasting with no obvious hair grow out	Cannot completely cover gray
Permanent	Oxidation/ reduction reaction	Darken hair color, cover gray	Permanent	Excellent coverage of gray hair	Color is permanent
One-step bleaching	Oxidation/ reduction reaction	Lighten hair color, cover gray	Permanent	Achieve light blonde hair shades	Damaging to hair
Two-step bleaching	Oxidative alkaline reaction	Dramatically lighten hair color, cover gray	Permanent	Achieve dramatic hair color lightening	Very damaging to hair

the hydrogen peroxide in bleaching or permanent waving products, resulting in rupture of the hair shaft. Hair that has been treated with a gradual hair colorant must therefore grow out before other dyeing or waving procedures are used to guarantee an optimal result [32].

25.5.4 Temporary

Temporary hair coloring agents comprise only 3% of the hair coloring market and are removed in one shampooing [43]. They are used to add a slight tint, brighten a natural shade or improve an existing dyed shade. Their particle size is too large to penetrate through the cuticle, accounting for their temporary nature [12]. However, the dye can be easily rubbed off the hair shaft and can run onto clothing if the hair gets wet from rain or perspiration. Temporary hair dyes do not damage the hair shaft and may be used by persons who are allergic to paraphenylenediamine. These dyes are most popular among elderly women who wish to achieve platinum hair. This is accomplished by adding a bluish or purplish temporary rinse to the hair after shampooing to cover yellow hues in the hair created by small amounts of remaining eumelanin or pheomelanin.

They contain acid dyes of the same type used to dye wool fabrics and belong to the following chemical classes: azo, anthraquinone, triphenylmethane, phenazine, xanthenic or benzoquinoneimine [58]. These dyes are known as FDC and DC blues, greens, reds, oranges, yellows, and violets. No damage is imparted to the hair shaft by these dyes making them appropriate for men and women of all hair types.

25.5.5 Semipermanent

Semipermanent dyes are retained in the hair shaft by weak polar and Van der Waals attractive forces, thus lasting through 6–10 shampooings [13]. Usually, 10–12 dyes are mixed to obtain the desired shade [38]. Semipermanent dyes produce tone-on-tone coloring rather than effecting drastic color changes, so their role is actually in toning rather than dyeing hair. The less the color change required by the patient, the more satisfied he or she will be with the semipermanent dye result. Semipermanent dyes are best suited for patients with less than 30% gray hair that want to restore their natural color [60]. This is done by selecting a dye color that is lighter than the natural hair color since the dye will penetrate both the gray and the nongray hairs, resulting in an increased darkening of the nongray hairs. It is not possible to lighten hair with semipermanent dyes, since they do not contain hydrogen peroxide, nor is it possible to darken hair more than three shades beyond the patient's natural hair color. Thus, in the cosmetic industry, semipermanent dyes are known as suitable only for staying "on shade."

25.5.6 Permanent

Permanent hair coloring is the most popular hair coloring technique on the market today accounting for 85% of hair dyes sold for both professional salon and home use. Three out of every four dollars spent on hair dyeing in the United States is for some type of permanent hair dye. Permanent hair coloring is so named because the dyestuff penetrates the hair shaft to the cortex and forms large color molecules that cannot be removed by shampooing [51]. This type of hair coloring does not contain dyes, but rather colorless dye precursors that chemically react with hydrogen peroxide inside the hair shaft to produce colored molecules [14]. The process entails the use of primary intermediates (*p*-phenylenediamines, *p*-toluenediamine, *p*-aminophenols) which undergo oxidation with hydrogen peroxide. These reactive intermediates are then exposed to couplers (resorcinol, 1-naphthol, *m*-aminophenol, etc.) to result in a wide variety of indo dyes. These indo dyes can produce shades from blonde to brown to black with highlights of gold to red to orange. Variations in the concentration of hydrogen peroxide and the chemicals selected for the primary intermediates and couplers produce this color selection [61]. Red is produced by using nitroparaphenylenediamine alone or in combination with mixtures of *para*-aminophenol with metaphenylenediamine, alphanaphthol or 1,5-dihydroxynaphthalene. Yellow is produced by mixtures of orthoaminophenol, orthophenylenediamine and nitro-orthophenylenediamine. Blue has no single oxidation dye intermediate and is produced by combinations of paraphenylenediamine, phenylenediamine, methyltoluenediamine or 2,4-diaminoanisole [45].

Permanent dyeing allows shades to be obtained both lighter and darker that the patient's original hair color. Higher concentrations of hydrogen peroxide can bleach melanin thus the oxidizing step functions both in color production and bleaching. Due to the use of hydrogen peroxide in the formation of the new color molecules, hair dyes must be adjusted so that hair lightening is not produced with routine dyeing [11]. However, hydrogen peroxide cannot remove sufficient melanin alone to lighten dark-brown or black hair to blonde hair. Boosters, such as ammonium persulfate or potassium sulfate, must be added to achieve great degrees of color lightening. The boosters must be left in contact with the hair for 1–2 h for an optimal result. Nevertheless, individu-

als with dark hair who choose to dye their hair a light blonde color will notice the appearance of reddish hues with time. This is due to the inability of the peroxide/booster system to completely remove reddish pheomelanin pigments, which are more resistant to removal than brownish eumelanin pigments.

25.6 Permanent Waving

25.6.1 History

The idea of making straight hair permanently curly is not new. The first permanent hair waving procedure was developed by Nessler in 1906 and consisted of a borax paste applied to the hair followed by the use of external heat in the form of electrically heated hollow iron tubes. Later it was refined by combining the borax paste with heat generated by a chemical heating pad attached to the curling rods with a clamp. Temperatures reached about 115°C and heating continued for 10–15 min [27]. Unfortunately, this procedure was very damaging to the hair. The idea of the cold permanent wave was introduced in the 1930s and immediately replaced the heat wave method. The cold waving solution contained ammonium thioglycolate and free ammonia at a controlled pH. This technique was patented in the United States by McDonough on June 16, 1941. Interestingly enough, this cold wave solution, with slight variations, is still popular today for both salon and home use. It is estimated that more than 65 million permanent waves are sold in salons and 45 million home waves are performed on an annual basis in the United States [57].

25.6.2 Technology

The chemistry of the permanent waving process is based on the16% cystine incorporated into disulfide linkages between polypeptide chains in the hair keratin filament. These disulfide linkages are responsible for hair elasticity and can be re-formed to change the configuration of the hair shaft. Permanent waving utilizes three processes: chemical softening, rearranging, and fixing of the disulfide bonds [56]. The basic chemistry involves the reduction of the disulfide hair shaft bonds with mercaptans [6, 62]. Table 25.8 lists the basic ingredients in a waving lotion and their intended function.

Once the hair has been thoroughly saturated with the waving lotion, the hair is placed under a plastic shower cap. The cap traps the heat of the body, which is used to increase the activity of the permanent wave solution. The cap also traps the smell of sulfur, which is very characteristic in a salon where permanent waving is being performed. The sulfur smell, which resembles rotten eggs, is produced as sulfur escapes from the hair when the disulfide bonds are broken.

The processing time for the permanent wave depends on the thickness and condition of the hair. Coarse hair requires a longer processing time than fine hair due to the longer time required for the waving lotion to penetrate a thicker diameter hair. If the hair has been previously chemically processed and the cuticle disrupted, the processing time is shorter. For example, undyed hair requires a longer processing time than permanently dyed or bleached hair. In order to avoid over- or under-processing the hair, a "test curl" is checked to determine if the desired amount of curl has been obtained. The test curl is typically placed at the nape of the neck where the hair is the most resistant to permanent waving. This ensures that an adequate amount of curl has been achieved over the entire scalp. A successful test curl has been achieved when the hair retains a "C" shape when the curler is removed. If the hair is not in a "C" shape, the permanent wave solution must be left in the hair for longer to cause more bonding breaking to occur.

Once the desired amount of curl has been achieved, the hair disulfide bonds are re-formed with the hair in the new curled conformation around the curling rods. This process is known as neutralization, fixation or "hardening." The neutralization procedure, chemically characterized as an oxidation step, involves two steps. First, two-thirds of the neutralizer are applied to thoroughly saturate the hair with the rods in place and allowed to set for 5 min. The rods are then removed and the remaining one-third of the neutralizer is applied for an additional 5 min. The hair is then carefully rinsed [27].

A permanent wave is designed to last 3–4 months. The final appearance of a permanent wave is determined by the size of the mandrels around which the hair was wrapped. Very tight curls, such as pin curls, are achieved by wrapping the hair around small curling rods. Pins curls are popular among mature women wishing to use the tight curl to add body and create the illusion of fullness with thinning hair. Conversely, loose waves, such as body waves, are achieved by wrapping the hair around large curling rods. Body waves are used to create wavy rather than curly hair.

There are several types of permanent waves depending on the tightness of the wave and the chemistry of the solution employed. The differences between the various types of permanent waves are due to the unique attributes of the waving lotions. Waving lotion consists primarily of a reducing agent in an aqueous solution with an adjusted pH [23]. The most popular reducing agents are the thioglycolates, glycerol thioglycolates, and sulfites. On the basis of waving lotion type, permanent waves can be classified into the groups listed in Table 25.9 [18, 62].

Table 25.8 Permanent waving lotion ingredients

Ingredient	Chemical examples	Function
Reducing agent	Thioglycolic acid, thiolactic acid, glycerol monothioglycolate, sodium sulfite	Break disulfide bonds
Alkaline agent	Ammonium hydroxide, triethanolamine	Adjust pH
Chelating agent	Tetrasodium EDTA	Remove trace metals
Wetting agent	Fatty alcohols, sodium lauryl sulfate, disodium laureth sulfosuccinate, sodium laureth sulfate, cocoampho-diacetate	Improve hair saturation with waving lotion
Antioxidant	Tocopherol, tocopherol acetate	Preservative
Buffer	Ammonium carbonate	Adjust pH
Conditioner	Proteins, humectants, quaternium compounds	Protect hair during waving process
Opacifier	Polyacrylates, polystyrene latex	Opacify waving lotion

Adapted from Lee AE, Bozza JB, Huff S, de la Mettrie R: Permanent waves: an overview. Cosmetics and Toiletries 103:37–56, July 1988 [27]

Table 25.9 Types of permanent waves

Type of permanent wave	Chemistry	pH	Advantages	Disadvantages
Alkaline	Ammonium thioglycolate or ethanolamine thioglycolate	9–10	Quick processing time, tight curls	Harsh on hair shafts
Buffered alkaline	Ammonium bicarbonate added to alkaline curl ingredients	7–8.5	Less harsh on hair than alkaline perm	Less harsh than alkaline perm, but still damaging
Exothermic	Thioglycolate and peroxide to produce dithiodiglycolate	6.5–7	Heat produced for patient comfort	Must be properly mixed to prevent hair damage
Self-regulated	Dithioglycolic acid and thioglycolate-	6.5–7	Stops processing automatically at equilibrium	Not good for hard to perm hair
Acid	Thioglycolate esters, such as glycerol mono-thioglycolate	6.5–7	Less damaging to hair	Produces looser, shorter lasting curl
Sulfite	Sulfite or bisulfite	6–8	Less odor	Long processing time, harsh on hair

25.6.3 Alkaline Permanent Waves

Alkaline permanent waves utilize ammonium thioglycolate or ethanolamine thioglycolate as the active reducing agent in the waving lotion. The pH of the waving lotion is adjusted to 9–10 since the thioglycolates are not effective at an acidic pH. Alkaline permanent waves produce tight, long-lasting curls very rapidly. The amount of time to produce the curl is known as the "processing time." Thus, alkaline permanent waves have a short processing time. They are not a popular wave however, since the hair is left inelastic and harsh. The alkalinity of the per-

manent wave produces hair shaft swelling, which irreversibly damages the cuticle. This can be problematic in individuals with color-treated hair, especially bleached hair. To minimize hair damage, the concentration of the alkaline thioglycolate waving lotion is adjusted from 7% for natural hair to1% for bleached hair.

25.6.4 Buffered Alkaline Permanent Waves

The high pH of the alkaline permanent wave can be reduced to minimize unnecessary hair damage. This has led to the development of the buffered alkaline permanent wave. In order to decrease hair swelling encountered from high-pH alkaline permanent waves, a buffering agent, such as ammonium bicarbonate, is employed to reduce the pH to 7–8.5. This allows rapid production of a tight curl long-lasting curl with less hair damage.

25.6.5 Exothermic Permanent Waves

Another variation on the permanent wave, known as an exothermic permanent, is designed to increase patient comfort by reducing the chill from the cold waving solution. The heat is produced as a by-product of the chemical reaction when the oxidizing agent, such as hydrogen peroxide, is mixed with the thioglycolate-based waving lotion immediately prior to scalp application. The reaction of the thioglycolate with the peroxide produces dithiodiglycolate, the disulfide of thioglycolate, which limits the extent to which the permanent wave can process. These products are only available for professional use, since irreversible hair damage can occur if the waving lotion is not properly mixed with the oxidizing agent prior to application.

25.6.6 Self-Regulated Permanent Waves

One of the major problems for the hair stylist who performs permanent waves is getting to each client as soon as the processing time is completed. It is not unusual for a busy hair stylist to have three to four permanent waves processing at the same time. This need has led to the development of self-regulated permanent waves, designed to limit the amount of hair disulfide bond breakage. Over processing, due to leaving the permanent wave solution on the hair longer than recommended, causes extensive hair damage. If the permanent wave solution is left on the hair for an extended period of time, it can weaken the hair to the point that it may act like a depilatory, breaking all of the bonds such that the hair can be wiped away. Self-regulated permanent waves are designed to form a chemical equilibrium such that the disulfide bond breakage is stopped. This is accomplished by adding dithioglycolic acid to the thioglycolate-based waving lotion. This is the same chemical reaction discussed for exothermic permanent waves.

25.6.7 Acid Permanent Waves

Acid permanent waves, as opposed to alkaline permanent waves, are designed with an acidic waving lotion at a pH of 6.5–7. They are based on thioglycolate esters, such as glycerol monothioglycolate. The lower pH produces less hair shaft swelling, thus hair damage is minimized. These products result in a looser, shorter-lasting curl, but leave the hair soft. They are ideal for bleached or color-treated hair. It is possible to achieve a tighter curl if the permanent wave is processed with added heat under a hair dryer, but more hair shaft damage results. In general, tighter curls produce more hair damage and looser curls produce less hair damage.

25.6.8 Sulfite Permanent Waves

Sulfite permanent waves are mainly marketed for home use and have not found popularity among salons in the United States. These products differ in that the reducing agent is a sulfite or bisulfite, instead of a mercaptan. This accounts for the reduced odor, which is their primary advantage. They require a long processing time at a pH of 6–8 and result in loose curls. A conditioning agent must be added to the formulation as the sulfite permanent waves can leave the hair feeling harsh.

25.7 Permanent Hair Straightening

Hair straightening is a common practice among individuals with kinky hair [2]. The hair can be straightened with heat or chemical techniques [29]. Heat straightening techniques are temporary. This section discusses the permanent method of hair straightening, also known as lanthionization [49].

25.7.1 History

The first permanent hair straighteners, also known as hair relaxers or perms, were developed around 1940 and consisted of sodium hydroxide or potassium hydroxide mixed into potato starch. Once the disulfide bonds were

broken, the hair was pulled straight and the disulfide bonds re-formed in their new configuration.

25.7.2 Technology

Hair relaxing, also known as lanthionization, is a chemical process whereby extremely curly hair is straightened using metal hydroxides, such as sodium, lithium, potassium, or guanidine hydroxide, by changing about 35% of the cysteine content of the hair to lanthionine along with minor hydrolysis of the peptide bonds [22]. Chemical relaxing can be accomplished with lye-based, lye-free, ammonium thioglycolate, or bisulfite creams [6].

Lye-based, or sodium hydroxide straighteners are alkaline creams with a pH of 13. Sodium hydroxide is caustic substance that can damage hair, produce scalp burns, and cause blindness if exposed to the eye. These products are generally restricted to professional or salon use and may contain up to 3.5% sodium hydroxide [48].

Lye relaxers are available in "base" and "no-base" forms. The "base" is usually petrolatum that is applied to the scalp and hair line prior to application of the sodium hydroxide. This prevents scalp irritation and burns. The "base" relaxers contain between 1.5% and 3.5% sodium hydroxide and therefore require that the scalp and hairline be coated with a petrolatum base prior to application. These higher concentration lye products are necessary for hard to straighten hair. "No-base" relaxers, on the other hand, contain 1.5%–2.5% sodium hydroxide and only require base application to the hairline [25]. They are more popular since it is time consuming for the beautician to apply the base to the scalp and most individuals are re-straightening hair that has already been chemically weakened.

Other strong alkali chemicals sometimes used in place of sodium hydroxide are guanidine hydroxide and lithium hydroxide, which are known as "no-lye" chemical hair straighteners. These relaxing kits contain 4%–7% cream calcium hydroxide and liquid guanidine carbonate. The guanidine carbonate activator is then mixed into the calcium hydroxide cream to produce calcium carbonate and guanidine hydroxide, the active agent. These products do not require basing of either the scalp or the hairline. A comparison of lye and no-lye hair straighteners is presented in Table 25.10.

Thioglycolate can also be used as an active agent in hair straightening [33]. These are the same thioglycolate chemicals that were described as permanent wave solution, except that they are formulated as thick creams, rather than lotions. The cream adds weight to hair and helps to pull it straight. Also, instead of the hair being wound on mandrels, it is combed straight while the thioglycolate cream is in contact with the hair shaft. Thioglycolate hair straighteners are extremely harsh on the hair and are the least popular of all the relaxing chemicals for this reason. The thioglycolate cream has a pH of 9.0–9.5, which removes the protective sebum and facilitates hair shaft penetration. Chemical burns can also occur with this variety of chemical hair straightener [5].

The least damaging of all hair straightening chemicals are the ammonium bisulfite creams. These products contain a mixture of bisulfite and sulfite in varying ratios depending on the pH of the lotion. Many of the home chemical straightening products are of this type, but can only produce short-lived straightening.

Table 25.10 Comparison of lye and no-lye chemical relaxers

Hair quality	Lye chemical relaxer	No-lye chemical relaxer
Relative strength on scale of 1–3 (higher no. is stronger)	3	1
Alkaline relaxing agent	NaOH or KOH	Guanidine hydroxide
Chemical agent	OH	OH
pH	12.5–14	12.5–13.5
Hair shaft penetration	Faster	Slower
Processing time	Shorter	Longer
Irritation	High	Low
Hair drying potential	Less drying to hair and scalp	More drying to hair and scalp

Adapted from Obukowho P, Birman M (1995) Hair curl relaxers: a discussion of their function, chemistry, and manufacture. Cosmet Toilet 110:65–69 [31]

Summary for the Clinician

Hair cosmetics are important for health and appearance issues. Shampoos minimize the incidence of scalp cellulitis and seborrheic dermatitis through the combination of anionic, cationic, amphoteric, and nonionic detergents. The excessive removal of sebum by the shampoo leading to unattractive, unmanageable, frizzy hair can be counteracted through the use of instant, deep, and leave-on conditioners. Hair as a form of personal expression is made possible through a variety of hair styling products to include sprays, gels, waxes, mousses, pomades, and brilliantines. Finally, dyeing, permanent waving, and straightening chemical procedures can alter the actual appearance of the individual hair shaft. Thus, hair cosmetics combine issues of hygiene and appearance.

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Chapter 26

Natural Products for Hair Care and Treatment

26

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Synonyms
phytotherapy

Key Features

- There has been an explosion in the use of natural products for hair care and treatment.
- An efficient follicular delivery system is key to enhancing the effectiveness of these natural products.
- The industry is challenged to chemically characterize natural constituents, understand their bioactivity, and thereby assure safe and effective use.

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26.1 Natural Products for Hair Care and Treatment

Natural products have become popular for the treatment of many ailments, and for boosting the immune system. They have also been incorporated into cosmetics and hair care products because of their beneficial effects and as a source of chemical ingredients for specific functions. The consumer public's interest is growing, reflected by their increased purchasing of natural products and the explosive growth of the industry.

Some perspective on this explosion may be helpful. A good source of information on what ingredients are used is the *International Cosmetic Ingredient Dictionary and Handbook* [16]. This four-volume set represents 33 years of continued effort to establish and maintain a nomenclature system for ingredients used in cosmetics. The various chemical classes of ingredients used in cosmetics are listed in Table 26.1.

Other functional cosmetic ingredients that may be used in hair care products include antidandruff agents, antistatic ingredients, fragrances, emulsion stabilizers, preservatives, surfactants, and viscosity controlling agents.

Another way of looking at the explosion of products is to consider how many ingredients are used in the various product categories [16] and how many products are in each category as reported to the Food and Drug Administration [14] (Table 26.2).

The natural-based products are interpreted by the public as being safer than synthetic products. Pharmaceutical, clinical and internet publications claim that there is an expansion of natural product uses clinically, but there are limited in vitro and in vivo studies and fewer human studies. In addition, there are no large multicenter clinical studies of the efficacy of these bioactive ingredients [43, 44, 45].

The safety of such natural chemical ingredients is under government regulation in most countries.

In the United States, products for hair care and treatment are regulated by the Food and Drug Administration (FDA) under the authority of the Food, Drug and Cosmetic Act (FD&C Act) enacted in 1938 (Note: the original authority, the 1906 Pure Food and Drug Act, did not include any authority to address cosmetics.) Products claiming a medical benefit (e.g., antidandruff) are considered as drugs according to the FD&C Act and may be regulated as over-the-counter drugs or as prescription drugs. When a product is considered a drug, then both safety and effectiveness must be demonstrated. Products asserting improvements in appearance are generally considered cosmetics. The law requires simply that manufacturers should have data demonstrating the safety of ingredients used in cosmetics.

Table 26.1 Chemical classes of ingredients used in cosmetics

Type of cosmetic	Number of ingredients
Hair colorants	293 individual ingredients
	2 natural, including henna
Hair conditioning agents	1970 individual ingredients
	136 natural, including ginkgo biloba
Hair fixatives	240 individual ingredients
	4 natural, including rice bran extract
Hair waving/straightening agents	47 individual ingredients
	6 natural, including orchid extract

More specifically, the law states that a cosmetic product refers to any substance or preparation intended for application to any external surface of the human body or to the teeth or buccal mucosa, wholly for the purpose of cleaning, perfuming or protecting them, or keeping them in good condition or changing their appearance or combating body odor or perspiration except where such cleaning, perfuming, protecting, keeping, changing or combating is wholly for the purpose of treating or preventing disease.

In the book *A Century of Consumer Protection*, former FDA Chief Counsel Tom Scarlett wrote a chapter on cosmetics regulation [36] entitled "The least of FDA's problems." In his discussion he makes the point that, "unlike drugs and medical devices, whose therapeutic effectiveness is important to health, cosmetics have a less vital role...yet another factor is that cosmetics, unlike drugs, can be made to achieve their desired results through the use of safe ingredients...a product with more ambition than a cosmetic would require more potent ingredients that could have adverse effects."

While the above asserts that cosmetics can be made with safe ingredients, it remains a wise course of action to review the data supporting that an ingredient is safe. In the United States, the Cosmetic Fragrance Toiletry Association, with the support of the FDA and the Consumer Federation of America, has backed a successful 30-year voluntary safety program, Cosmetic Ingredient Review (CIR), which has reviewed and published in peer-reviewed journals on the safety of ingredients used in cosmetic products. The major accomplishment of the CIR has been its impact on the cosmetic industry, which strives to follow CIR's conclusions, with the result

Table 26.2 Ingredients used in cosmetics

Cosmetic product category	Number of ingredients
Baby shampoos	189 individual ingredients/29 individual products
	18 natural ingredients
Bleaches	108 individual ingredients/120 individual products
	3 natural ingredients
Color sprays	22 individual ingredients/5 individual products
	4 natural ingredients
Dyes and colors	598 individual ingredients/1690 individual products
	42 natural ingredients
Conditioners	660 individual ingredients/651 individual products
	130 natural ingredients
Rinses	148 individual ingredients/62 individual products
	11 natural ingredients
Adult shampoos	727 individual ingredients/916 individual products
	135 natural ingredients
Permanent waves	351 individual ingredients/260 individual products
	15 natural ingredients
Straighteners	108 individual ingredients/63 individual products
	3 natural ingredients
Hair tonics	522 individual ingredients/598 individual products
	111 natural ingredients

that cosmetic products of enhanced safety are available to the consumer.

Since this discussion is focused on natural products, a word of caution based on the CIR's experience is warranted. A major concern of this panel has been the lack of chemical characterization of the plant parts used, the method of extraction, the presence of contaminants, and the documentation of ingredients' biological activity on skin and hair [8].

Phytotherapy (natural) refers to novel bioactive ingredients derived from plants. Popular ingredients include Chinese herbs, vitamins, minerals, antioxidants, enzymes, hormones, and a multitude of "naturals." Plant extracts are often poorly chemically defined because they are so complex and each part of the plant, i.e., stems, seed, flower, and fruit, contains numerous complex chemicals. Other factors adding to the complexity of the chemical ingredients include the geographic area in which they are grown, the quality of the soil and the inherent pesticides and metals within that soil (contaminants) [47], the quality of plant collection and storage processes, and impurities related to the extraction process. The natural products usually contain numerous chemical ingredients, such as the active ingredients, antioxidants, vehicles, pH adjusters, stabilizing ingredients, preservatives, fragrances, and other ingredients, e.g., nutrients and plant enzymes. Adding to the dilemma of chemical characterization is that it differs according to the part of the plant as well as the species. Even natural antimicrobial activity can be derived from natural ingredients and used in a cosmetic product for stabilization or as a preservative. The plant extracts differ from synthetic purified chemicals in that they are more complex mixtures of chemical ingredients. The actual

natural hair care products contain a mixture of plant, animal, and synthetic chemicals, and share a common purpose with the regular (synthetic) hair care products.

There is continuing investigation of bioactive ingredients that can rejuvenate skin and hair, and promote hair growth. This chapter gives an overview of the ingredients used in natural hair care products and their potential use.

The natural chemical ingredients are appropriately incorporated into many skin and hair care products, e.g., shampoos, conditioners, hair styling products, hair colorants, permanents and relaxers, hair promoters, and antiparasitic therapies, according to the function required. Indeed, natural chemicals do provide many of these functions; for example, antioxidants, proteins, saccharides, glycerides, acids, alcohols, saponins, alkaloids, antimicrobials, nutrients, vitamins, essential oils, sterols, flavonoids, and enzymes. The natural plant ingredients are also of therapeutic benefit in hair conditioning, hair growth stimulation, hair colorants, for scalp dermatitis such as seborrheic dermatitis and as antiparasitic and antimicrobial agents.

26.2 Important Natural Ingredients that Possibly Promote Hair Growth

There are many hair growth stimulants patented for use in hair growth or hair tonic products for the treatment and prevention of alopecia. It remains unclear how these products produce their effects, but claims suggest that hair growth is secondary to the acceleration of blood flow, activation of the anagen dermal papillae, dihydrotestosterone inhibition, anti-inflammatory activity, and increased nutrition.

Many natural hair care and hair growth promoter products include a multitude of vitamins, antioxidants, amino acids, proteins, and fatty acids, specifically vitamin E, vitamin C, vitamin A, niacin, flavonoids, amino acids, fatty acids, and polyphenols.

26.2.1 Hair Promoters

26.2.1.1 Asiasari

An extract of *Asiasari radix* showed the potential for hair growth stimulation with increased protein uptake in a mouse study, and an in vitro study of human follicles revealed the expression of vascular endothelial growth factor (VEGF) in human dermal papillae. These results suggest the hair-promoting potential of *Asiasari* extracts [33]. This ingredient is not currently listed as a cosmetic ingredient [16], and no cosmetic uses have been reported to the FDA [14].

26.2.1.2 Proanthocyanidins

Proanthocyanidins are extracted from grape seeds. In vitro, they have been shown to promote hair follicle cells and convert the telogen follicle to an anagen follicle [40]. The mechanism of action may be inhibition of the transforming growth factor TGF-beta1 [21]. The nomenclature of the grape seed extract used in cosmetic products is Vitis Vinifera (Grape) Seed Extract [16] and that is the name that should appear on the ingredients list in a cosmetic product. Two uses of grape seed extract were reported to the FDA, neither in a hair care product [14].

26.2.1.3 Ginkgo Biloba

Ginkgo biloba leaf extract in an in vitro study promoted hair growth through effects on proliferation and inhibition of apoptosis of follicular cells [23]. Ginkgo Biloba Leaf Extract is the nomenclature for this ingredient in cosmetics [16]. It is reportedly used in five cosmetic products, including three hair care products [14].

26.2.1.4 Aloe

Aloe vera L or *Aloe barbadensis* gel has been used traditionally for the treatment of alopecia, with improvement [17]. Aloenin is the major ingredient [20]. The CIR program [12] completed a safety assessment of cosmetic ingredients derived from the aloe plant. These ingredients function primarily as skin conditioning agents and are included in cosmetics only at low concentrations. The aloe leaf consists of pericyclic cells, found just below the plant's skin, and the inner central area of the leaf, i.e., the gel, which is used for cosmetic products. The pericyclic cells produce bitter yellow latex containing a number of anthraquinones, phototoxic compounds which are also gastrointestinal irritants responsible for cathartic effects. The CIR concluded that anthraquinone levels in the several *Aloe barbadensis*/*Aloe vera* extracts available are well understood and can conform to the industry-established level of 50 ppm. Insufficient data were available to assess the safety of extracts from other aloe species.

The CIR also advised the industry that the total polychlorinated biphenyl (PCB)/pesticide contamination of any plant-derived cosmetic ingredient should be limited.

26.2.1.5 Proteins

Cysteine enhanced hair growth in a mouse screening study to evaluate the hair-growth-promoting effects of plant extracts. The extracts were painted on the backs of mice for 30–45 days and protein synthesis was measured using the cysteine uptake assay, using cultured murine vibrissae follicles. In addition, the immortalized human keratinocyte line and dermal papillae were evaluated using thymidine incorporation assays. With this method several growth factors involved in hair growth were seen to increase [33]. Cysteine is listed as a cosmetic ingredient [16] with functions that include hair conditioning and hair waving/straightening. Nine uses of cysteine are reported in cosmetics, eight of which are in hair care products [14].

26.2.1.6 Bergamot

In another mice study, bergamot and boxthorn applied topically increased the cutaneous activity of superoxide dismutase, collagen, and decreased malondialdehyde with an observable increase hair growth [38]. Citrus Aurantium Bergamia (Bergamot) Fruit Oil and Leaf Oil are both listed as cosmetic ingredients [16], with the Fruit Oil functioning in cosmetics as a fragrance and the Leaf Oil as an astringent. Bergamot oil is reportedly used in 51 cosmetic products, two of which are hair care products [14].

26.2.1.7 Chinese Herb

In a 6-month randomized, double-blind trial in 396 males with androgenetic alopecia the Chinese herb extract "Dabao" was applied topically and resulted in modest hair growth as compared to the placebo (42% compared to 37%) [22]. This ingredient is not currently listed as a cosmetic ingredient [16], and no cosmetic uses have been reported to the FDA [14].

26.2.1.8 Ginseng

Ginseng radix in the form of a 70% extract of red ginseng (steamed and dried roots of Panax ginseng C.A. Meyer, a type of Ginseng Radix) showed the potential to promote hair growth on cultured mouse vibrissal hair follicles. The major extract [gensenoside-Rb (1) or G-Rb (1)] exhibited activity while other extracts are ineffective [24]. Panax Ginseng Root Extract is a cosmetic ingredient [16] that functions as a skin conditioning agent. Ginseng extract is reportedly used in 344 cosmetic products, 118 of which are hair care products [14].

26.2.1.9 Henna

Henna or *Lawsonia alba* L. (Lythraceae) has been recognized and used as a hair promoter since Egyptian times. Henna has mild anti-inflammatory activity and analgesic effects. Henna is listed as a cosmetic ingredient [16] with the function of a colorant/hair colorant. There are 29 uses reported, 25 of which are in hair care products [14].

Henna use is also widespread in tattooing and while this falls outside the scope of this chapter, a note of caution is appropriate. In 2004, the CIR reaffirmed the safety of *p*-phenylenediamine as a hair dye ingredient; CIR did agree with FDA that other uses of this dye are unapproved. The CIR expressed particular concern over the practice of combining *p*-phenylenediamine with henna (so-called dark henna) for use in temporary tattoos – *p*-phenylenediamine is a known sensitizer, highly inappropriate for such use as evidenced by reports of severe adverse skin reactions to dark henna temporary tattoos. The Panel urged users to report adverse reactions to the FDA (for more information, see http://www.cfsan.fda.gov/~dms/cos-tatt.html).

26.2.1.10 Hibiscus Extract

In vivo and in vitro studies evaluated petrolatum ether extracts of the leaves and flowers of *Hibiscus rosa-sinensis* for its potential to stimulate hair growth. Topical preparations were applied to the backs of albino rats and to cell cultures of hair follicles from albino rat neonates. From the study it was determined that, compared to the flower, the leaf extract was a more potent hair promoter [2]. Hibiscus-derived extracts (from several species) are listed as cosmetic ingredients [16] with a variety of functions ranging from colorant to skin conditioning agent; there is one mention of its use as a lytic agent. There are 34 uses in cosmetic products reported, 27 of which are in hair care products [14].

26.2.1.11 Hydrangea

Hydrangea macrophylla extract promotes hair growth through the suppression of TGF-beta, which delays the catagen cycle. The mechanism may be accounted for by the fact that TGF-beta is activated by caspase in the lower portion of the follicle and the outer layer of the outer root sheath. This mouse study suggests that TGF-

beta suppression could be used to treat alopecia [46]. Hydrangea-derived extracts (from several species) are listed as cosmetic ingredients [16] whose primary functions are skin conditioning agents. There are no reported uses in cosmetic products [14].

26.2.1.12 Illicium

Illicium anisatum has been shown to increase blood flow in a mouse model. In an in vitro study of mouse vibrissae follicles, a water-soluble extract of *Illicium anisatum* leaves, fruits, and roots (shikimic acid and glycosides, and polysaccharides) produced better growth than controls. Similar acetone extracts inhibited the growth of hair follicles. Shikimic acid induced insulin growth factor-1, keratinocyte growth factor, and VEGF in the hair follicle. The results of this study suggest that *Illicium anisatum* water extract could be a useful additive to hair growth products [34]. Illicium Verum (Anise) Fruit Extract, Fruit Powder, and Oil are all listed as cosmetic ingredients, but there are no listings for extracts of *Illicium anisatum* as a cosmetic ingredient [16]. Eight uses of anise are reported in cosmetics, none of which are in hair care products [14].

26.2.1.13 Sorphora

In a mouse study, the topical application of an extract of *Sophora flavescens* dried root induced increases in growth factors such as insulin-like growth factor-1 (IGF-1) and keratinocyte growth factor (KGF) in dermal papillae cells and inhibited type II, 5-alpha-reductase activity. This result suggests that sorphora has potential as a natural hair growth promoter [32]. Sophora Flavescens Root Powder is listed as a cosmetic ingredient [16] with functions ranging from abrasive to fragrance to skin protectant. No uses in cosmetics are reported [14], although derivatives from *Sophora angustifolia* and *Sophora japonica* are currently used in cosmetics.

26.3 Natural Hair Growth Promoters with DHT Inhibitory Activity

Some of the over-the-counter botanical (natural) hair promoters incorporate minoxidil as an active ingredient. An internet search reveals that many of these products are available, such as Nioxin® Intensive Therapy Follicle Booster, and Scalp Med® Vitadil-5Aand Vitadil-2A.

The majority of plant DHT inhibitors contain saw palmetto, liposterolic extract of Serenoa repens and beta-sitosterol, azelaic acid, zinc, B6, linoleic acid, and polyphenols. Some of these available internet products are Avacor®, ProCede®, Provillus® and Rivivogen®.

26.3.1 Natural Fatty Acids with DHT Inhibition

A number of natural ingredients have some antiandrogen activity, primarily inhibition of 5-alpha-reductase. The active ingredients include fatty acids, for example gamma-linolenic, linoleic, palmitic, elaidic, oleic, and stearic acids. In a mouse study, an acetone extract of *Boehmeria nipononivea* exhibited 5-alpha-reductase inhibition and a hair growth effect [39]. The CIR has completed a review of the safety of fatty acids (oleic, lauric, palmitic, myristic, and stearic) as used in cosmetic products [13], with the conclusion that these ingredients are safe to include in cosmetics under present practices of use and concentration. That conclusion was reaffirmed in 2005 [4].

26.3.2 Saw Palmetto

In a double-blind clinical trial, six out of ten patients with androgenetic alopecia improved when treated with Saw palmetto, a liposterolic extract of *Serenoa repens*, and beta-sitosterol [30].

26.4 Natural Ingredients that Retard Hair Growth

Soymilk reduces hair growth and reduces hair fiber diameter. Soybean trypsin inhibitor (STI) and Bowman-Birk protease inhibitor (BBI) are two serine protease inhibitors isolated from soybeans; BBI inhibits trypsin and chymotrypsin. These inhibitors reduced hair growth, hair diameter, and pigmentation in a mouse model and in human studies [37].

26.5 Natural Hair Conditioning – Repair of Damaged Hair

Sage is known as a healing herb. There are over 500 species of *Salvia* from which sage is extracted. The type of sage used for cooking and skin and hair care is *Salvia officinalis* L. It is known as common sage, true sage or garden sage. It is used as a hair conditioner and is noted to enhance hair's appearance. The major ingredients of

sage extract are tannins, saponins, borneol, and camphor [9].

26.5.1 Oligosaccharides

Cotton honeydew extract is composed of a combination of oligosaccharides such as fructose, glucose, l-inositol, melezitose, saccharose, trehalose and trehalulose. These ingredients are protective of the hair fiber, by smoothing the cuticle scales. In controlled studies cotton 1% honeydew was superior to placebo [27].

In comparison studies, coconut oil is superior to mineral oil and sunflower oil in reducing protein loss from hair. Coconut oil is composed of triglyceride (lauric acid, a fatty acid) that has an affinity for hair proteins. Because of its low molecular weight and straight linear chain, it is able to penetrate the hair. In contrast, mineral oil, a hydrocarbon, has no affinity for hair while sunflower oil, a triglyceride (linoleic acid), is double bonded and does not penetrate the hair [31].

The essential oils from plants impart a pleasant aroma, shine, and conditioning effects, emolliency and they also improve the elasticity of skin [1].

26.6 Natural Hair Color

26.6.1 Henna

Henna or *Lawsonia alba* L. (Lythraceae) has been recognized and used as a hair promoter since Egyptian times. Henna has mild anti-inflammatory activity and analgesic effects [3, 48].

Vegetable dyes are natural colors that basically coat the hair fiber with minimal penetration and are considered to be non-oxidizing dyes. These hair dyes have been used for centuries. In the past there were problems with the stability of natural hair dyes, which easily oxidize causing the color to fade. This has been remedied with the addition of some synthetic stabilizers. The primary vegetable dyes are henna and walnut. The different shades of color are achieved by adding other plant leaves.

The henna dye (lawsone) is obtained from the leaves of *Lawsonia inermis* and imparts a reddish color. The dye binds strongly to the hair, probably due to the binding of thiol groups to keratin [3]. The variations of color are achieved by adding the dyes from other plants as well. Onion (*Allium cepa*) imparts a copper color; apigenin, a flavonoid from many plants (chamomile flowers), imparts a yellow color; curcumin, from the spice turmeric, gives a range of color from yellow to deep orange [11, 42]; red sorrel, *Hibiscus sabdariffa*, gives a red color. These dyes [26] and the henna dyes [15] have low allergic potential.

26.7 Natural Ingredients for the Treatment of Seborrheic Dermatitis

Seborrheic dermatitis is an inflammatory disorder which presents as erythematous and scaling dermatitis of seborrheic areas, including the scalp, mid-face trunk and intertriginous areas. It commonly has associated superficial folliculitis with a yellow greasy scale or only erythema and fine scaling. A Wood's light examination (blue UVA light) will identify colonization of *Pitysporium* organisms, which fluoresce orange under the light due to porphyrins from the organism. This disorder is commonly treated with antidandruff shampoos, which are obtainable as an over-the-counter item or as a prescription drug. Important synthetic ingredients are zinc pyrithione, ketoconazole, imidazoles, ciclopirox olamine, and low potency corticosteroids, selenium sulphide, and tar. These ingredients have several, e.g., anti-inflammatory, antifungal, and exfoliative, activities [1].

Effective phytotherapeutic agents include extracts of sage, rosemary, thyme, garlic, and walnut.

26.7.1 Sage

Sage (*Salvia officinalis* L.) is an old favorite, and the extract is massaged into the scalp to control dandruff and to treat alopecia. Sage contains vitamins A, C, and B-complex, and high amounts of calcium and potassium. Salvia Officinalis (Sage) Extract, Flower/Leaf/Stem Extract, and Leaf Extract are listed as cosmetic ingredients [16] with functions as fragrances, skin conditioning agents, and oral care agents. There are 139 uses in cosmetic products reported, 70 of which are in hair care products [14].

26.7.2 Rosemary

Rosemary (*Rosmarinus officinalis*) is used as a tonic or rinse to remove oil (seborrhea), and to add volume and shine to the hair. Rosmarinus Officinalis (Rosemary) Extract, Flower Extract, Flower/Leaf/Stem Extract, and Leaf Extract are listed as cosmetic ingredients [16], with functions that include antioxidant, deodorant, skin conditioning agent, fragrance, and antimicrobial. There are 339 uses in cosmetic products reported, 166 of which are hair care products [14].

26.7.3 Thyme

Thyme (*Thymus vulgaris* L.) is also used to treat dandruff and as a hair growth promoter. It is again used in rinses and tonics and frequently mixed with sage and rosemary. Thymus Vulgaris (Thyme) Flower/Leaf Extract and Leaf Extract are listed as cosmetic ingredients [16] with functions that include fragrance, skin conditioning agent, and skin protectant. There are 27 uses in cosmetic products reported, 14 of which are hair care products [14].

26.7.4 Garlic

Garlic (*Allium sativum* L. Liliaceae) has been used for centuries for its antiseptic, antioxidant, anti-inflammatory [7], antibacterial, and antifungal effects [6]. When garlic is placed directly on the skin it induces an irritant reaction and occasionally a contact allergy. It is diluted in hair products as a lotion, which is applied to the scalp to reduce seborrheic dermatitis. Allium Sativum (Garlic) Bulb Extract and Oil are listed as cosmetic ingredients [16] with functions as skin conditioning agents, flavorings, and fragrances.

There are 13 uses in cosmetic products, with 10 of those in hair care products [14].

26.7.5 Walnut

Walnut (*Juglans regia* L. Juglandaceae) leaves have been used to treat skin rashes, acne, alopecia, scalp dermatitis, and seborrheic dermatitis. In an emollient it has been used for its antipruritic action and as a protective barrier. Black walnut (*Juglans nigra*) is used primarily for seborrheic dermatitis [10]. Juglans Regia (Walnut) Leaf Extract is listed as a cosmetic ingredient [16] with fragrance and skin conditioning functions. There are ten reported uses, all in hair care products [14].

26.7.6 Tea Tree Oil

Tea tree oil (melaleuca oil) is an essential oil extracted primarily from the leaves of *Melaleuca alternifolia*, a scrub-like tree in Australia. It is composed of mixture of hydrocarbons and terpenes, consisting of almost 100 ingredients. It has antimicrobial activity against *Pitysporum ovale*. In a double-blind study of patients with seborrheic dermatitis, 5% tea tree oil shampoo was as equally effective as ketoconazole shampoo. A recent report by Henley et al. [18] linked prepubertal gynecomastia in three boys to topical application of products containing lavender and tea tree oils. Melaleuca Alternifolia (Tea Tree) Leaf Oil is listed as a cosmetic ingredient [16] with antioxidant and fragrance functions. There are 52 uses reported in cosmetic products, 11 of which are in hair care products [14].

26.8 Natural Ingredients for the Treatment of Lice

The development of botanical lice-removal shampoo containing 0.05% paw paw, thymol, and tea tree oil effectively removed all lice and nits in a small study (n=21) [25]. These three ingredients inhibit adenosine triphosphate (ATP) production and lead to depletion of ATP stores, and ultimately they are anti-sarcoptic, antimicrobial, and antifungal.

Paw (*Asimina triloba* Dunal) has been shown to be effective against pesticide-resistant head lice. The active ingredients of paw are asimicin and trilobacin; thymol is the major component of the essential oil of *Thymus vulgaris*, whereas 1-terpinen-4-ol is the major active ingredient in tea tree oil from *Melaleuca alternifolia*. All three of these chemical ingredients are antimicrobial, antifungal, and anti-sarcoptic agents that have been shown to be safe and effective; they are now available in one product, called Paw Paw Lice Remover shampoo, from Nature's Sunshine Products (Rovo, Utah) [25, 35].

CIR's safety assessment of thymol as a cosmetic ingredient determined that it is safe for use in cosmetics at concentrations up to 0.5% [5]. Thymol is reportedly used in 14 cosmetic products, 3 of which are hair care products [14].

Custard apple from *Annona squamosa* Linn. is a traditional folk medicine for lice. It is prepared as a 20% w/w oil in water cream and was found to be an effective ingredient that cleared >99% of lice in 3 h [41].

26.9 Contact Dermatitis

Botanical contact dermatitis is poorly documented but with the rising use of botanicals in skin and hair care products, more contact dermatitis, irritant or allergic, can be anticipated. Those botanicals used in hair care products that have been linked with contact dermatitis are: aloes, cucumber, rosemary, sage, and tea tree oil. Natural fragrances have caused contact dermatitis and because of growing indices the more common antigens have been added to patch test screening trays. The fragrance mix contains jasmine absolute, ylang-ylang, narcissus absolute, sandalwood absolute, and spearmint oil.

If a product is clinically suspected, whole products can be used in patch testing [28, 29].

Summary for the Clinician

Plant and animal sources of chemicals offer a wide range of possible active and basic chemical ingredients that are needed to manufacture skin and hair cosmetics. The cosmetics industry is challenged to chemically characterize these plant and animal constituents, to remove the contaminants, and to understand these bioactive chemicals and find a safe use for them. The bioactive activities in dermatitis, hair growth, hair retardation, and coloring, and the phytotherapies for lice continue to be active areas of research. For the bioactive chemicals, an efficient follicular delivery system is needed [19, 45] that would enhance their effects. The greatest need however is to create a safe product whose therapeutic and cosmetic claims are founded on a good scientific basis.

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Chapter 27

Hair over the Ages and in Art – The Culture, and Social History of Hair and its Depiction in Art

27

Norbert Haas

Key Features

- Ancient world.
- Greek and Roman antiquity.
- The Western World Middle Ages.
- Renaissance.
- The wig's century.
- Nineteenth and twentieth centuries.
- Hair styles in non-European cultures.

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27.1 Introduction

From the beginning of recorded history, people have placed importance on their appearance. Styling one's hair seems to be an innate desire of human beings to emphasize their beauty and power. Since hair is a key aspect of one's appearance, grooming, styling, adorning, and removing hair were common practices in all societies. As reviewed here, hairstyles were influenced by preceding cultures, by religion, by those depicted for gods and emperors, by aspects of lifestyle such as sports, fashion, and the desire to display inner feelings. Further aspects include limiting signs of aging, revealing one's rank, identifying people by gender, and complying with cultural and religious mores (or, conversely, showing nonconformity). The focus of this overview is on the cultural history and social-historic aspects of hair.

Throughout history, hairstyles have been depicted in the visual arts, such as in sculpture, portraiture, and paintings. Artists of all epochs and painters in particular were especially interested in depicting human hair as a mean of expressing their own individual feelings or those of their time. On the other hand, art itself influenced the various types of hairstyles until modern times, when hairstyles became increasingly reflected in the mass media due to the rise of photography and film in the course of the twentieth century.

27.2 Ancient World

There is evidence to suggest that people of the metal Ages took great care with their appearance. The hairstyles were often sophisticated, with braids, hairnets, and ornaments being used by women, or with the hair cut straight at the shoulder in a bob.[1] Hairdress equipment was common in Late Bronze and Early Iron Age

1 As for the girl in the grave at Egtved, Denmark.

graves, and the mirror was a favored object among both the Celtic people and Scythian warriors. These objects and evidence from well-preserved graves show people as well-groomed individuals who shaved regularly, and braided or cut their hair. Bronze Age peoples used tweezers for plucking facial hairs, and hair ornaments were made with great craftsmanship.

In early societies the hairstyle worn by the common people was long or cropped usually held in a band. Aristocrats developed more complex styles. Sumerian noblewomen, for example, contained their hair in rolls and plaits around the head. They also powdered it with gold dust and adorned it with golden ornaments.[2] Babylonian and Assyrian men dyed their long hair black, whereas Persian nobles stained theirs red with henna. Slaves and prisoners in ancient cultures had shaved heads.

The ancient Egyptians must have taken considerable effort to maintain their appearance and beauty. In addition to an abundance of informative paintings, we find combs and hairpins in their graves. They used hair extensions and dyed wigs in a variety of colors. Blue, green, blonde, and gold colors were preferred, though black wigs hued by indigo were the favorite. Nearly every adult Egyptian, both man and woman, wore some kind of wig, while children had their own distinctive hairstyle. Women's wigs tended to be longer and larger than men's. They were composed mostly of human or horse hair (Fig. 27.1). Since wigs symbolized a form of monumentalism and conservatism, the Pharaohs never appeared in public without a wig. They also shaved their faces and wore stiff false beards. The process of hairdressing was well-structured and part of a large-scale ritual. Hairdressers were highly esteemed and had their place on the right and left side of the Pharaoh's throne. Egyptian art is the richest source of wigs in history. Astonishingly, the official hairstyle stayed more or less the same over a period of nearly three thousand years. Egyptian styles, including hairstyles, had several revivals in later periods of time.[3]

In the bible we find impressive tales on the topic. Absalom, favorite son of King David, was defeated and killed in "the forest of Ephraim" having caught his long hair in an oak tree (2 Samuel 13-19). Similarly, Samson met his doom because of his hair. In the story of Samson and Delilah, Samson's hair is the core of his strength and vitality (i.e., his long uncut hair because of his vow). Delilah, a Philistine, coaxed him into revealing that the secret of his strength was his long hair. She took advantage of his confidence to betray him to his enemies (Judges 16). Another example is the prophet Ezekiel who cut his hair performing a symbolic act to illustrate the impending fate. We do not know details of the old Hebrew hairstyles because the Hebrew religion did not allow the depiction of god or the human body.



Fig. 27.1 Painted limestone statues of Prince Rahotep and his wife, Nofret. Egyptian Museum, Cairo (reproduced from Das Grosse Buch der Kunst. Bildband Kunstgeschichte Lexikon, published by Westermann, Braunschweig 1958)

27.3 Hairstyles in Greek and Roman Antiquity

Greeks regarded hair as a vehicle for personal expression, along with a strong interest in physical fitness and personal appearance. Hair was associated with strength and purity. Greeks let their hair grow. They saw it as a source of life and gave sacrifices of hair to the dead, e.g., Achilles (Iliad XIII, 134).

Minoan women had long black hair that fell to the shoulders and even to the waist. The hair of both sexes was worn looped and braided and dressed with jewels, pearls, and ribbons. Girls and young dancers wore their hair in a style that now is known as the ponytail. People in various cultures have worn this hairstyle ever since. In Aegean art, males are depicted with single or double plaits. Homer's heroes had such hair, as did the warriors at the battle of Marathon (490 bc). During

2 Information on hair during Ancient times mostly stems from archeological finds, including tombs.

3 In the 1960s, the film *Cleopatra*, with Elizabeth Taylor starring in the title role, brought renewed interest in this style.

the Archaic period (i.e., up to about 500 bc) the male youth or kouros (Grk) wore his waist-length hair finely braided – an extremely artificial time-consuming style of the privileged classes.

After the Persian Wars ended, men throughout Greece wore simpler hairstyles. Long hair was seen as a symbol of eastern influence. Historically, trimming hair has also been attributed to sporting activities. This "athlete" hairstyle, where the ears were not covered with hair, spread to Italy. A terracotta head of a stylish young man from a Greek colony in Southern Italy (Fig. 27.2) exhibits hair growing upwards in short crops, obviously fixed in position with a form of hair gel. It is reminiscent of portraits of Alexander the Great (356–323 bc), whose famous anastole, i.e. ascending locks from a central parting, became the model. He was also the first Greek king not to wear a beard – which became a symbol of youth. Thereafter, with the exception of philosophers, it became unfashionable to wear a beard for several centuries.

Noble Greek women must have devoted a great deal of time each day to styling their hair. The maiden of the Archaic period, the kore (Grk), wore extremely fine braids. The representation of the figure's hair evolved, from the early solid mass hanging at the sides and back of the head to the separation of the top and sides into tresses. By the fifth century however, a clear gender difference occurred. In contrast to men, women continued to wear long hair, usually curled on the forehead and sides of the head and drawn into a bun at the nape. Later a very distinct youthful style was in fashion, the so-called melon.[4]

Hair jewelry had been known since the time of Homer, who described the strings, nets, and circlets decorating Andromache's hair (Iliad XXII, 468). Gifts in graves show that wreaths in the shape of leaves, made of silver or even gold and ivory curlers and hair pins, were in use as well. Later, fine hairnets were in use. They were made of pure gold and studded with jewels such as rubies or pearls. Dyeing, bleaching, curling or straightening of hair was common, and curling irons were used to create elaborate hairstyles. Grooming products such as fragrant oils, lotions, and pomades were used to add shine. During the Hellenistic period, women used ribbons and cloth bandeaus in their hair. Curls and braids were arranged in elaborate settings. Hair was colored using ashes or henna, and even colored bee's wax was used, resulting in rather shrill hairdos.

Antique iconography gives an insight into the habits, fashions, and ideas concerning hair, since Greek artists created statues of the gods according to rules, albeit variable but rather consistent over centuries [23]. Thus, many of the ancient gods can be identified by distinct hairstyles, as described by Winckelmann[5] and these served as models for human hairstyles throughout antiquity. Zeus, the main god, typically has his hair aligned in an upward, followed by a downward sweep, which then radiates outwards forming a corona of individual strands [14]. Asclepius, the healing god, is the only god to wear his hair similarly to Zeus! He also appears as a mature bearded man, but with a milder expression [8]. Aphrodite (Venus), Greek goddess of love and beauty, personification of Grace, had drawn back, straight hair with a bun on the crown. Hephaestus (Vulcanus), ill-matched consort of Venus, had his hair unkempt. His rough hairdo and that of Pan, a very common subject in ancient art,[6] were antithetical to that of Apollo, who represented culture and sophistication.

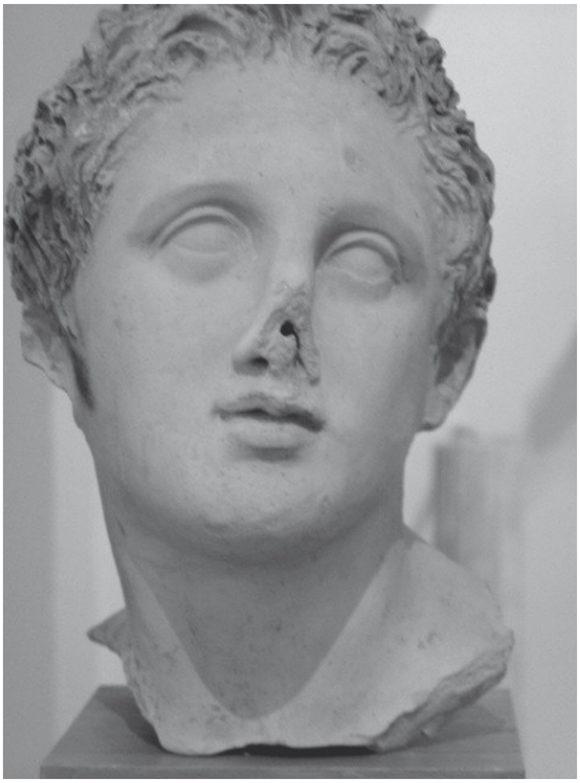


Fig. 27.2 Greek youth (Museum of Antiquities, Berlin)

4 Named because the hair was divided into a number of segments running like the ribs of a melon from the forehead to the back of the head.

5 Johann Winckelmann (1717–1768), German archeologist and art historian.

6 Represented with horns and ears of a goat.

Since Homer, baldness has been seen as a sign of ugliness (Iliad II, 218). Bald-headed Socrates compared his looks with that of the silens, followers of Dionysus (Bacchus, god of wine) who had an ivy wreath to cover androgenetic alopecia. Their Italian counterparts were the Fauns, creatures of the wild, part man and part beast, characterized by a Faun tail (sacral hirsuties) [24]. The ancient Greek physician, Hippocrates, was the first to report that eunuchs fail to become bald. The wreath of permanent hair encircling the back and sides of the head is sometimes referred to as the Hippocratic wreath.

Greek adolescent and grown-up males shaved their body hair as seen on most classic Greek statues.[7] H.W. Siemens[8] maintained that it depicted a state of non-physiological alopecia. He denounced this type of hermaphroditic ideal and that it might manipulate the western ideal of beauty [20].

The Roman civilization strongly emphasized "proper" grooming as a sign of character as well as social status, age, and religion. In austere republican Rome, prior to 300 bc, hair does not seem to have been trimmed. For men, a simple and natural hairstyle prevailed. Similarly, women wore simple long hair that was tied to a juvenile knot or a matron's bun. When the Greek style toilette became fashionable, more complicated hairstyles were adopted.

Historical insight about hair and hairstyles comes from works by historians and playwrights. Romans learned to change their natural hair color. Red coloring was provided by substances from ashes. Brown and "blond" tones were achieved by mixtures such as "spuma batava" (imported from what is now the Netherlands), as reported by Pliny the elder, a scientist and critic. Men plucked their gray hair or applied pitch-black dyes.[9] The use of wigs for nightly excursion was recorded by Petronius, author of the comic novel Satyricon. Blond hair taken from female prisoners of war from Germanic tribes became fashionable, as did black hair pieces imported from countries as remote as India. Romans must have loved to spend their time in the barber's shop, a frequent motif of the comedy of the time [11].

The imperial dynasties markedly influenced contemporary hairstyles since their portraits and coins were distributed throughout the provinces. The neatly cropped hair of the young emperor Augustus, combed into a fringe on the forehead, set a new trend and was varied only by his successors. The hallmark of portraits of Augustus is a naturalistic classicism. The rendering of his features and the forking of his hair above the brow is individual. Tiberius and Claudius had regular frontal curls. Nero's curls were corrugated with crimping tongs and carefully piled on each other in several rows (as branded by Sueton). Emperor Titus' head was a curly tangle. According to Martial, these curls were also painted on the scalp if necessary, and in sculptures the curly tangle was the result of numerous drill holes in the marble headpiece (Fig. 27.3). Emperor Trajan (ad 98–117), in conscious contrast, let his hair simply drop militarily in strands onto the forehead. The second century emperor Hadrian was the first bearded Roman emperor, a fashion that was maintained by his successors. Portrait statues of Hadrian's Bithynian favorite, Antinoüs, reveal a model of youthfulness with locks falling into his face.

Imperial ladies began to wear increasingly complicated hairstyles. During the Flavian dynasty (69–138 ad), high-ranking Roman ladies preferred a hair style composed of piled-up curls which became continuously higher, ending in tower-like masses constructed with toupees and probably iron wires for support (Fig. 27.3). This is the style that Juvenal, the most powerful of all Roman satiric poets, mocks when he describes "the woman who appears like Andromache from the front but quite the opposite from the back."

In the late Imperial period hairstyles were simpler again,[10] as was the case during the early Christian era. The apostle Paul condemned long hair as non-Christian, saying, "Does not nature itself teach you that for a man to wear long hair is degrading to him, but if a woman wears long hair it is her pride?"(1 Corinthians 11,14).[11] In the late-antique portraiture curls of the second century baroque have been banished in favor of hair that is combed forward on the brow in rigid, striated locks, or skullcap treatment of the hair and a schematic handling of the emperor's beard. Finally, the clean-shaven faces of Constantine the Great and his successors in a hieratic, transcendental style were the hallmark of Byzantine and medieval iconography.

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7 Fine examples are those by Lysippus. The best is that of the "Apoxyomenos" (Vatican museum), a young male athlete, scraping and cleaning his oil-covered skin with a strigil. There is remarkable precision of detail, especially in the hair.

8 German dermatologist (1891–1969) renowned for the eponym "epidermolysis bullosa Hallopeau–Siemens."

9 Martial, a Roman playwright, jeers at someone "who very suddenly changed from a swan into a raven" (Epigrams III, 43).

10 Revival of the "melon" style

11 It was only with the rise of Christianity, and 600 years later Islam, that modest covering became compulsory. St. Paul wrote to Timothy "that women should adorn themselves modestly and sensibly in seemly apparel, not with braided hair…" St. Peter expressed similar views.



Fig. 27.3 Flavian lady (Museum of Antiquities, Berlin)

27.4 The Middle Ages in the Western World

Christianity was to become the dominating force in political, cultural, and daily life during the Middle Ages.[12] The Christian faith had gradually spread all over Europe and was adopted by the people of the Roman Empire as well as by those in Northern and Eastern Europe. When the Roman Empire declined in the west, Germanic tribes came to power and formed the upper classes of society.

Germanic tribes let their long hair and beards flow as a sign of male dignity and liberty, in contrast to the ancient Gauls, who were part of the inhabitants of the Roman Empire and tied their hair up at the neck.[13] Early in the Middle Ages, free people wore their hair long and styled in waves or loose curls. A center part was common. Royal power had a sacred aspect. Merovingian kings were known as the "long-haired kings." They did not cut their hair from childhood until death [19]. Portrait sculpture (plastic art) no longer existed, so little detail is known.

From the early Middle Ages and in different parts of Europe folk and fairy tales tell of long-haired maidens, such as Rapunzel and Lorelei. In "Rapunzel," a young woman is trapped at the top of a tower. She manages to gain her freedom by letting her very long hair down for her lover to climb up. The story of "Lorelei" might date back to the German myth.[14] It tells of sirens living in the water of the Rhine river and the golden hair that entices sailors to their death. In Slavic mythologies, a fairy such as the Lithuanian laum appears as a beautiful naked maiden with long fair hair. An early English chronicle is the source for the story of Godiva.[15] While stories of hairy men go back to the Orient and the Bible,[16] in the Middle Ages the fairy tales of "the wild man" may represent a magic interpretation of the sign of hypertrichosis universalis[17] [17, 18].

From the ninth century on, nobles on the Continent again wore short hair. This fashion was strongly influenced by the Byzantine hairstyle as seen on the German emperor Otto III, son of a Byzantine princess in medieval illustrated manuscripts. The Byzantine Empire, the eastern part of the former Roman Empire which existed until 1453, was Christendom's cultural great power with far-reaching effects on fashions and art. Masculine hairstyles were short, and men were mostly clean-shaven. Byzantine ladies wore veils and often encased their long hair in a silk cap or a pearl net. Elaborate hair jewelry was characteristic of Byzantine dress of the upper classes.[18] Some of these fashions came to Europe via France,

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12 The popes supported bans of long hair among the population and of beards among the clergy.

13 As best known from the comic strip Asterix by illustrator A. Uderzo.

14 The Loreley (also spelt Lorelei) is a large rock on the bank of the Rhine River. The rock produces an echo and is associated with the legend of a beautiful long-haired maiden who threw herself into the Rhine in despair over a faithless lover and was transformed into a siren. Loreley has been the subject of a number of literary works and songs; the poem "Die Lorelei" by Heinrich Heine (1797–1856) was set to music by more than 25 composers.

15 Anglo-Saxon gentlewoman famous for her legendary ride while nude through Coventry, her hair covering all of her body except her legs.

16 For example, of Esau, elder brother of Jacob, who at birth, was red and hairy.

17 The sign of hypertrichosis universalis was interpreted differently. There are examples of magic and religious interpretation in mythology and fairy tales representing the original animal character.

18 In the figures of saints in Byzantine mosaic technique, the material for faces is chiefly natural stone, its gentle gradations contrasting spectacularly with colored glass tesserae of the hair.

the dominating power of the time. Byzantine hairdress also strongly influenced that of Eastern Europe, especially the Balkans and Russia.

The Christian religion had an increasing influence on hairstyle: a typical example of the influence of the church is the tonsure, a shaved patch on the head which indicated the change of status from lay to clerical.[19] Monks, such as those of the order of Carthusians, wore hair shirts. Monastic styles symbolized religious devotion, humility, and personal renunciation. Furthermore, the church, always concerned about modesty, encouraged women to veil their long plaits. Curly and long hair was regarded as a symbol of freedom, adventure, and independence. It was considered immoral for women, which led to styles in which hair was contained and kept under various kinds of coverings. Only unmarried young women were allowed to show their hair curled openly while a married woman, in public, wore head draperies hiding her hair. In the late Middle ages, i.e., the thirteenth and fourteenth centuries, men's hair was neatly rolled at the neck in a page boy style.[20] In public, however, on official events, men also were obliged to wear a hat or a cap. In conclusion, hairstyle and headgear may be regarded as indicative of the religion and the social structure of medieval society [19].

At the beginning of Occidental painting, pictures were full of the ideas of early Christianity and hardly ever showed other than biblical motives [1]. Romanesque sculpture in early periods of medieval art, known to us from relief compositions over church portals, show Lord Jesus and the apostles wearing long hair and beards which are depicted in an extremely stylized way, while Gothic sculpture achieved a greater degree of realism (Fig. 27.4). The main subject in Byzantine art is the Blessed Virgin with child. The hair of Holy Mary is strictly veiled in icon painting, whereas in the medieval religious art of Western Europe, Holy Mary, symbolizing all women, is shown with long hair [1]. On a famous painting by van Eyck in the Louvre, Nicolas Rolin,[21] the powerful chancellor of Burgundy, is kneeling opposite the Holy Mary with golden-brown falling curls.

The women of Rolin's time, fashionable ladies of Northern Europe, shaved and plucked their hairline to make their foreheads seem higher, as depicted in quite a few paintings including the blessed Virgin. What was considered to be an important physical feature during this era is for H.W. Siemens an "alopecia triangularis" and the result of a "sick" ideal of beauty [22]. A high forehead in adult women may also have resulted from bleaching and coloring the front hair (with noxious substances?), which was common in those days [12]. Descriptions of "false" alignment of hair in statues of St. Mary Magdalen[22] by Tilman Riemenschneider [13, 14], or alopecia[23] in paintings of leprosy patients may be of interest to trichologists [16].

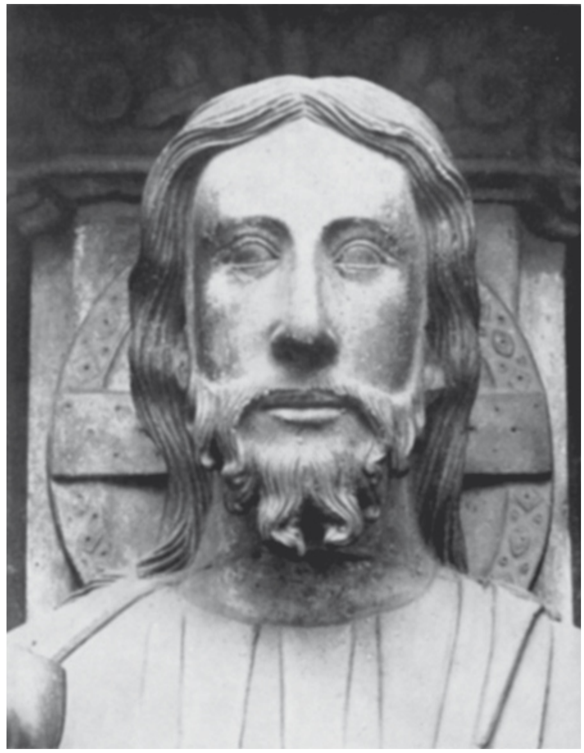


Fig. 27.4 Christ, from cathedral in Chartres (approx. 1210 ad). (Reproduced from Die Kunst der Völker, published by Herder-Verlag, Freiburg, 1940)

19 In the early Middle Ages, monks were performing minor surgery. When the church forbade clergymen to occupy themselves with activities that involved blood, the barbers, or Barber-surgeons, as they were called, provided medical care and formed guilds. Interestingly, in the mid 1200s, the two major companies of Parisian barbers were named after the patron saints of physicians – St. Cosmas and St. Damian!

20 For women, a steeple headdress with a veil, the "Hennin," was fashionable in France and Flanders.

21 With neatly cropped short hair.

22 Who anointed Jesus' feet and wiped them with her hair (John 12:3–7).

23 Pathological loss of hair must have been more important for the person concerned, since wigs were out of fashion in Western countries during the Middle Ages.



Fig. 27.5 Portrait of Maximilian I by A. Dürer (1471–1528). Staatsbibliothek, Bamberg (reproduced from Albrecht Dürer 1471–1971, published by Prestel Verlag, Munich, 1971)

27.5 Renaissance Europe

The Renaissance was a time of heightened interest in art and beauty, with more freedom in hairstyles since religious control over daily life and art had diminished.

At the beginning of the sixteenth century, young men in Northern Europe were proud of their full long hair. The German emperor Maximilian I (1459–1519), known from a famous portrait by A. Dürer (Fig. 27.5), kept such a hairstyle throughout his life. However, fashions changed and men were beginning to wear short hair and to grow beards. The new style in appearance was influenced by monarchs, especially popular ones. It is said that the change was brought about after King Francis I of France (1494–1547) had accidentally burnt his long hair with a torch. His courtiers copied this look, and when his European colleagues, such as Charles V of Spain,[24] cut their hair, success of the new fashion was established.

English styles reflected the preferences of King Henry VIII and his daughter, Elizabeth I. The Elizabethan era increased attention given to personal appearance and hair care. English women, particularly those in the upper classes, followed personal grooming similar to the queen. One major trend was not to cover as much of a woman's hair as in the Middle Ages. The hair in the back was placed inside a net that rested above the collar. A high forehead was still much admired, so people continued to shave or pluck their hairlines. After Elizabeth ascended the throne, it became much more common for British women to use hair dyes, cosmetics, and perfumes. Many of her subjects imitated her reddish-gold hair. An aging Elizabeth concealed her balding head with a curly red wig. As a result, wigs became much more popular in England. Mary, Queen of Scots, also wore a wig.[25] This became known when she was beheaded and her wig remained in the hand of the executioner who wanted to show the head to the idle onlookers. It was not until the seventeenth century that the wig became a generally acceptable form of adornment or corrective for nature's defect [4, 19].

The persons and subjects chosen by the Italian Renaissance artists are mainly from antique history and mythology. From portraits by Sandro Botticelli and Piero di Cosimo, one can see, for example, that as early as the second half of the fifteenth century the elaborate decoration of women's hair with precious materials had become a real art, in which goldsmiths and craftsmen carefully worked out every line of the often extremely complicated ornamental design that had to harmonize with the movement of braids or unbound hair. Painters often used the women of the period with the most beautiful, very long, wavy thick hair that flowed down the back luxuriantly, reaching to or even covering the hips as models.[26] In his well-known painting "The Primavera" (Uffizi) Botticelli used the flowing hair draperies to suggest the movement of the figures. Similarly, the curls of Botticelli's angels are arranged in correspondence to the courtly coiffure of the time and are painted very carefully and accurately. In the Renaissance human hair is generally depicted in a most subtle and meticulous way [1]. For example, the hair of Renaissance sculptures was sometimes colored.[27]

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24 A portrait by Tizian is found in the Bavarian State Picture Galleries of Munich.

25 As a young maiden, by her remarkable beauty – she had red-gold hair – Mary summed up the contemporary ideal of the Renaissance princess.

26 Botticelli's "The Birth of Venus," a most famous picture, is considered by many experts to be the very epitome of the spirit of the Renaissance.

27 When the "Magdalen" by Donatello was damaged in the 1966 flood at Florence, restoration work revealed the original painted surface, including realistic flesh tones and golden highlights throughout the saint's hair.

The Mona Lisa (Louvre) by Leonardo da Vinci (1452–1519) set the standard for future portraits. The overall harmony achieved in the painting, including the sensuous curves of the woman's hair, make it an enduring record of Leonardo's genius. The painting was analyzed with the aim of finding possible pathologies including such of the hair [3]. In Dutch, Italian, and Spanish art, there are quite a few paintings that show alopecia areata, as reviewed by G. Borroni and W. Dotz [2, 5]. The rarity of iconographic evidence of alopecia may simply represent a form of censure of this condition which entails moral condemnation of the person affected [2].

27.6 The Wig's Century

The Baroque period, i.e., essentially the seventeenth century, is known as "the wig's century." For men, the wig fashion was set in 1624 by an aging king Louis XIII of France and was to remain popular for about 150 years. In the beginning, wigs were worn in order to hide baldness (as in the case of Louis XIII) and were therefore made in such a way as to simulate natural hair. Later they were refined and varied considerably in size, height, form and style as well as in color, and were no longer meant to hide missing hair but to replace natural hair. After King Louis XIV of France (1643–1715) had begun wearing long thick curls, others adopted that look, which went out of fashion again after his death. Men's wigs were mostly longer than women's. On peaces of art, such as marble or painted portraits, the huge wigs are a main feature. Many of the period's outstanding personalities, such as the philosopher Leibniz, the musician Bach, or the Austrian statesman Prince Eugen, are known to us from portraits with impressive wigs.[28]

The social importance of the wig was immense. The hairstyle was also a political issue, since the courtiers seem to have used the wig as a sign of participation in royal power. Political conflicts arose over hairstyles. The rebellion against the monarchy in England's civil war (1642–1651) was also a rebellion against the wigs. The Roundheads of Cromwell's army had their hair cut extremely short and derided the long curls and wigs of the Royalists. Similarly, religious sectarians such as the Puritans and the Quakers set themselves apart from other people by cutting their hair.

While wigs were the hairdo of the upper classes and officials, the Golden Age of the Netherlands, especially the 1630–1650s were a time of long locks. Men wore their hair, beautifully cared for, falling naturally onto the shoulders and down the back. Complementary to this coiffure was a large beaver, felt, or velvet hat. Women's hair was dressed high on the crown in a bun decorated with pearl ropes and with ringlets at the sides and brow.

In paintings of that period, natural hair is often used as a major component of the light reflexes and the dynamics in a composition. In this respect, the Flemish painter Peter Paul Rubens (1577–1640) was the greatest exponent of Baroque paintings' vitality and sensuous exuberance [1]. In Italian Baroque sculpture, Gian Lorenzo Bernini showed an unparalleled sensual awareness of the surface textures of skin and hair.[29] In Spain of the seventeenth and eighteenth centuries, demands for realism and an emotional stimulus to piety led to sculpture of human hair together with real fabric costumes. In the artwork of the time, e.g., in Dutch and Spanish paintings, hair was depicted so precisely that (trichological) diagnoses and differential diagnoses can be made[30] [9, 21].

During the reign of Louis XV of France (1710–1774) and through the influence on fashion by his mistress, Madame de Pompadour,[31] upper-class women started hiring artists to create hairstyles. Hairdos were comprised of, e.g., live birds in cages, waterfalls, cupids, and even naval battles complete with ships and smoke. That was when the term "hairdresser" was born, in contrast to former mere wig makers and barbers. By 1767 there were 1200 hairdressers working in Paris which exemplified the leading position of France in fashion.[32]

28 In the seventeenth century the wig attained its maximum development, covering the head and shoulders and flowing down the chest.

29 "Apollo and Daphne" demonstrate an astonishing illusion of flesh and hair.

30 H.W. Siemens demonstrated that patients from the Leprosarium did not have alopecia from leprosy, but rather they had favus. This is shown in the painting Governors of the Home for Lepers at Haarlem 1667 by Jan de Bray (Frans Hals Museum, Haarlem, the Netherlands), where a young Dutch man with a vivid scalp infection, almost certainly favus, is shown being cared for by three officials of a charitable home intended for leprosy sufferers, and also in a picture by B. Murillo (Madrid), which shows saint Elizabeth as directress of the Leprosorium, who shampoos children with favus.

31 The "pompadour" was a special style introduced by Madame de Pompadour. Women created the illusion of a mass of puffy hair with the front hair rolled back and the side hair up to meet it in a roll that is drawn high over the forehead. Dressing the hair with a pompadour was favoured in the early twentieth century.

32 The hairdresser's increasing popularity is reflected in the comic character of Figaro, who is the hero of *The Barber of Seville* (1775) and *The Marriage of Figaro* (1784), two comedies by the French dramatist de Beaumarchais. Both were adapted for the opera, the former by Gioacchino Rossini and the latter by W.A. Mozart.

In the eighteenth century, both men and women continued to wear wigs, but generally smaller and lighter ones, that were powdered white. A special form was the toupee.[33] Men's wigs, whether in law, the army, or navy, each had their own style and were worn throughout the West, until the American and French revolutions swept these away along with other symbols of social status.

27.7 From the Nineteenth to the Twenty-First Century

During the French Revolution in 1792, both men and woman cut their hair short and arranged it closer to the head.[34] This change was based mainly on new ideas, such as Rousseau's philosophy[35] and the renewed interest in antiquity and classicism.[36]

Men's hair in the Victorian era (1837–1901) was short and simply parted on the side or the middle, even to the point of the brush-like crew cut. Most men wore some variety of moustache, sideburns, or beard. Well-known examples are the "fly" of emperor Napoleon III of France (1808–1873) and the white long beard of Charles Darwin. Uncle Sam, a popular U.S. symbol, had wavy white hair and chin whiskers.

While short hair has remained the prevailing hairstyle for men till today, women's hair fashions changed considerably. In the early Victorian period ("Biedermeier" style), Greek knots came into fashion, further the chignon, with standing rolls or loops on the crown, held by ribbons and combs. A hairdo like that of the empress Eugenie of France,[37] composed of a complicated arrangement of side curls and locks, was very time-consuming, since natural-looking waves were still achieved by using heated irons.[38] Victorian hairstyles aimed to create a sweet, feminine look; and long, thick hair was admired. By the 1890s, a special type of wide pompadour known as the Gibson Girl hairstyle arose.[39] To gain this look, women piled their locks high in the front.

33 Also spelled toupet, a small hairpiece covering a bald spot.
34 Bonaparte wore his hair cut close – le petit tondu, the "little crop-head," as he was called.
35 J.-J. Rousseau (1712–1778) French philosopher, writer and political theorist whose treatises and novels inspired the leaders of the French Revolution and the Romantic generation.
36 Emperor Napoleon I as painted by J.-L. David (1748–1829), A.-J. Gros, and other painters.
37 Wife of Napoleon III.
38 The permanent wave was invented not before the turn of the twentieth century. Later, the cold wave, with chemicals, simplified the process.
39 Featured in illustrations by American artist C.D. Gibson (1867–1944).



Fig. 27.6 Drawing of a young man by G.H. Naeke (1786–1835). Kupferstichkabinett, Dresden (reproduced from Europäische Graphik von 1500 bis 1900, published by Pawlak, Herrsching)

In the period known as romanticism, long "natural" hair was fashionable also for men. In 1809 a number of young German painters living in Rome formed the Brotherhood of Saint Luke. They soon acquired the originally derisive nickname Nazarenes because of their affectation of a "biblical" style of dressing and their hair (Fig. 27.6). Later, in England, the Pre-Raphaelites were fascinated by luxuriantly flowing hair as a sensuous aspect of female beauty. The magnificent flowing hair of his mistress was praised by the French poet Ch. Baudelaire (1821–1867) in masterpieces of imagination such as "La chevelure". The French impressionist painter A. Renoir (1841–1919) excelled in depicting the luminosity of young woman's skin and hair full of sparkling color and light [1]. The designers of the Art Nouveau style[40] were fascinated with luxuriantly flowing strands of female hair, influenced by the English Pre-Raphaelite aesthetic.[41]

40 Such as A. Mucha (1860–1939), French jeweler, whose designs in jewelry and glass contributed significantly to the Art Nouveau movement at the turn of the century.
41 Particularly the work of Dante Gabriel Rossetti (1828–1882).

New, short hairstyles for women began to emerge after World War I. These hairstyles reflected women's changing roles. At first, only the most daring young women cut off their long hair. In 1920, the new "emancipated" woman, the flapper, demanded to be recognized as man's equal in all areas. She adopted a masculine look, bobbing her hair. The "bob" haircut was a radical change from the long, contrived styles that predominated in earlier eras, and emerged on the fashion scene in the late 1920s. Women of all ages were wearing shorter hair as a symbol of the new political and social emancipation. Celebrities and the mass media influenced trends more strongly as the century continued. A succession of short, head-clinging hairstyles inspired by film stars, such as the page boy of Greta Garbo, followed. Hollywood was a main inspiration on women's hairstyle. The movie *Gone with the Wind* inspired a new look for pulled back hair. Although her natural hair color was reddish-brown, actress Marilyn Monroe became a legendary "blond bombshell" and a cultural icon of the twentieth century.[42]

The 1940s was a time of glamour with hair either curled or styled up. In the 1950s the invention of curlers for waving made the very short, layered Italian cut for young, active, informal women that discarded hats possible. Popular first ladies in the USA have served as models for American women, e.g., Mamie Eisenhower's haircut known as "Mamie bangs." Jackie Kennedy (1929–1994) continued to popularize the "bouffant," a hairdo rising up und back from the head in a high round shape.[43]

Men's styles remained generally short until the 1960s. Back in the silent screen era, actor Rudolph Valentino had influenced a trend to a shiny appearance of hair. Rock star Elvis Presley's gleaming hairstyle with sideburns was copied by millions.[44] Extremely short hairstyles were the crew cut and the buzz cut.

In the 1960s a great shift in culture took place and was symbolized by a change in hairstyles. Little can be compared to the night when the Beatles first appeared on TV on the Ed Sullivan show: four mop-headed working class lads from Liverpool turned fashion on its head and shook generations.[45] Around the world countless young people emulated the band members' characteristic long hair. Mick Jagger and the Rolling Stones and others soon followed and long hair in men quickly became a sign of rebelliousness.[46] Hair became to symbolize a certain freedom, and choosing one's style embodied feeling of individualism and personal identity. The punk look, during the 1970s and 1980s, was associated with a movement in pop music and spread across continental Europe and North America. Shaved heads on men also became more popular. Although conservative hairstyles are still the norm, shaved heads can be seen more often in public as well as in certain workplaces, including hospitals.

During the last decades of the century, there was no longer a uniform or universal look in men's hair, and many men had individualized, styled hairdos that required the use of diverse hair styling products. Men's hair care became one of the fastest-growing sectors in the hair products industry.

Nowadays, hair fashion is democratic; differences between social groups of a society and between nations have nearly vanished. While some follow new fashions, others choose to wear conservative styles or a classic look despite changing trends. While celebrities such as singers, actresses, models, or television journalists often wear wigs,[47] people use their hair for self-expression (as well as a vehicle for gaining social acceptance). People have many options for selecting styles that express their personal tastes and that suit their lifestyle and personality. Though mass media, advertising, and the hair-care industry play an expanding role in shaping attitudes about appearance and beauty, most people in today's world base the decision about their hair on their own esthetic preferences

27.8 Hairstyles in Non-European Cultures

Recent decades are characterized by an expanding awareness of other cultures, hairstyles, and beauty. In contrast to the changes in Western societies, religious beliefs still play a major role in designating certain hairstyles in traditional Non-Western countries, as do social and economic forces.

American Indians have hair that is usually straight, coarse, and uniformly black.[48] Native Americans wore

42 Marilyn Monroe (1926–1962) was the world's most famous blonde; her look, which is instantly recognizable, has inspired other performers.

43 As first lady of the United States from 1961 to 1963, she strongly influenced trends in fashion. Millions admired the first lady's elegance and copied her hairstyles.

44 Relatively long, greased-back hair.

45 Beatlemania.

46 In 1967, the Broadway musical "Hair" featured characters known as "hippies," i.e., members of a counterculture movement identified by their long, flowing hair and headbands. Milos Forman followed with an film adaptation (1979).

47 Including colored ones as in ancient Egypt.

48 While the vast majority of Europe's inhabitants are of the Caucasoid geographic race, characterized by variability in hair colour and texture which allows for more variability in hairdos.

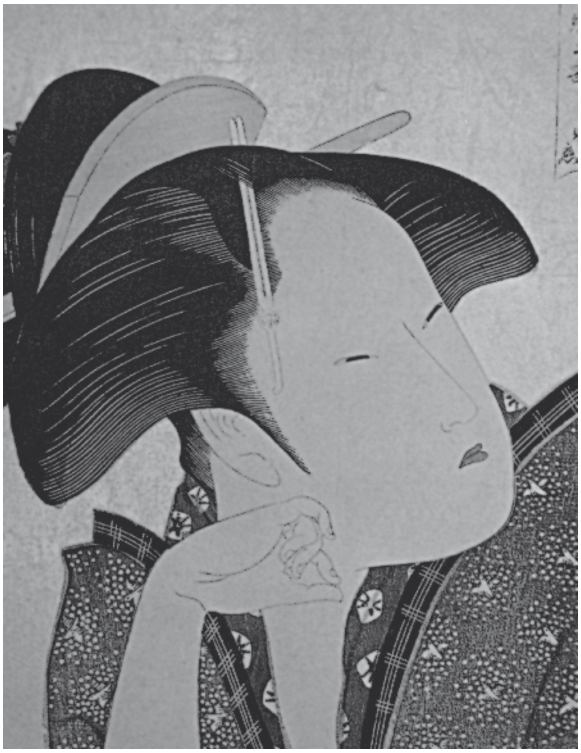


Fig. 27.7 Portrait of a woman. Woodcut by Utamaro. Musée Guimet, Paris (reproduced from Ukiyo-e Holzschnitte, published by Orell Füssli Verlag, Zürich, 1978)

their hair in diverse styles, influenced by tribal customs. Women grew their hair long, sometimes leaving it uncut their entire lives, regarding long hair as essential to their spirituality. Chiefs had distinctive and recognizable hairstyles. In the style known as the "Mohawk,"[49] men shaved off all but a ridge of hair that ran from the front to the back of the head. Iroquois men wore a "ridge" with feathers on top; other tribes were notable for carefully plucking all their facial and head hair, except for a scalp lock. Red Indian hairstyles play a role in the tales and myths of Northern America and only play a minor role in the arts.

Farther south in the Americas, more complex styles developed, such as the whorled arrangement of Hopi girls. Ancient Mexican women drew their hair into a bun or braided it with colored material and wound it around their heads. Mayan nobles appear to have shaved their skulls. Finds of antique masks, sculpture, gold works, and clay works provide remarkable insight into the lifestyles and hairstyles of the classic Mayan people.

49 Imitated by the so-called punks in the 1970s.

In China, men traditionally shaved the front hair and combed the back hair into a queue braided with horsehair or black silk.[50] The queue was a mark of dignity and manhood; to pull it was a great insult. Chinese women combed their hair back; unmarried girls wore long plaits. The communist revolution of 1949 brought strict directives. Men's hair was short, women's hair longer but uncurled. Nowadays, young people dye their hair red or blond and have adopted considerable looks of the West. In Chinese arts, hairs and eyebrows were regarded as a particularly expressive feature [7]. Wigs have been used in the traditional theatre of China and Japan.

In Japan, men traditionally shaved the front and top of the head, leaving a stiff pigtail at the back of the crown.[51] Women's hair in the medieval period streamed down their backs as celebrated in poems and other literary works. Geishas used lacquer (a precursor of modern-day hair spray) to secure their elaborate coiffures. Elaborate hairpins and combs were used by women of the geisha and courtesan classes during the Edo period (1603–1868). For centuries, hairstyles could indicate a person's marital status, social class,[52] occupation, and/or religious affiliation [10]. Special hairstyles were reserved for certain occasions, such as a traditional wedding or festivals. Recent trends point towards more Western styles including hair coloring. While the graphic arts of various cultures provide information about historic hairstyles in the eighteenth and nineteenth centuries, the various forms of traditional Japanese hairstyles have been masterly depicted by the decorative ukiyo-e style in the works of K. Hokusai (1760–1849), U. Hiroshige (1797–1858), and K. Utamaro (1753–1806) (Fig. 27.7). On ancient Japanese ceramic vases men appeared with an impressive alignment of hair, as described from a dermatologist's point of view by Maestri [14].

In India, hairstyle used to be widely influenced by religion. Sadhus[53] twist their hair in a knot on the top of their heads, whereas Sikhs[54] retain hair unshorn regarding hair as sacred. In Hinduism and Buddhism the tonsure dates back to Ancient times, indicating a renunciation of the world and a personal dedication to God.

50 The Manchu who ruled China from 1644 to 1911 were accustomed to braid their hair into a queue, or pigtail. When the Manchu conquered China they forced the Chinese to adopt this custom as a sign of loyalty to the new dynasty.

51 Japan's sumo wrestlers wear a version of ponytail that is oiled and then styled on the top of the head into a fan shape.

52 A distinctive men's hairstyle was worn, e.g., by members of the samurai (the warrior class).

53 Sadhu signifies any religious ascetic or holy man.

54 Indian religious group, living in the Punjab. The male Sikh is recognized especially by his practice of wearing his hair and beard uncut, the former being covered by a particularly large turban and the latter often restrained by a net.

As in other religions, where mourners demonstrate grief at the death of a person by alterations in hairstyle, long-haired Hindu widows cut off their hair. Hindu families follow the tradition of having a child's head shaved.[55] In South Asian arts, the subject matter of sculpture is almost invariably religious with a focus on the representation of the Hindu gods and the Buddha. Shiva usually has his hair well combed and knotted, a round dot on the forehead, or appears in an androgynous form with the hair piled in a hairdress of matted locks. Buddha's hair is long and stylized,[56] usually rendered by rows of small curls that hide the conical protuberance of the head.

Among Muslims, traditionally the hair was modestly concealed in public under the man's turban or fez. Men attended hammams (public baths) where they were shaved (sometimes the whole head except for the long topknot). There were also religious commandments concerning hair such as a single long lock on the shaved heads of Muslim men by which they believe Allah would pull them up to heaven. The pious pilgrim to Mecca cuts neither his hair nor his nails until the pilgrimage is over. Muslim women used to give their long hair a henna rinse and to cover it under a veil, and often continue to do so today for religious and political reasons. The Koran, the Holy book of Islam, prohibits the figuration and representation of living creatures. Consequently, plastic art as well as paintings of human hair are virtually nonexistent, except for a number of charming miniatures, such as by the Perso-Indian schools of miniature painting.

In Africa, the adornment of the human body involves all aspects of art. One of these is hairdressing, adapted to the kinky texture of African hair, which is done for its aesthetic value or to signal status, e.g., whether a woman is married, or to denote membership of various groups, including clans and tribes [15]. Different ethnic groups, such as the Nuba, the Massai, or the Yoruba, have long traditions of taking care of their hair, which they imbue with spiritual significance. Since the 1950s, Western hairstyles have been influencing traditional African ideas about hair, but traditions remain popular and many groups have retained their traditional hairstyle. As part of the black pride movement, Afro-Americans wear some version of the "Afro" (thick, tightly curled hair in a large, rounded shape, which is well suited to the texture of Afro-Caribbean hair) or have their hair styled in cornrows (three strands of hair tightly braided in a line along the scalp) or dreadlocks (hair that is twisted as it grows out of the scalp and left uncombed so that it forms rope-like locks).[57] Remarkable similarities with the so-called plica polonica have been noted [6]. In Africa, hairdressers enjoy a high status, while unkempt hair is seen as a sign of illness or antisocial behavior. Today, African hairdos are found worldwide, contributing to global hair-care products and service businesses [19]. In traditional and modern African art there are a variety of elaborate hairstyles depicted in designs such as wood sculpture, clay figures, pottery, portraits, and masks.

27.9 Conclusion

Ideas as to what constitutes attractive or appropriate hair have varied throughout the ages. As a result of the survey, religion and social status might be considered to be the two predominant factors that have influenced hairstyle throughout history. However, in Western societies, religion has lost importance, and political and social changes are gradually leveling the differences between social classes. In both Western and Non-European cultures, globalization and mass media are reducing the differences between nations, especially amongst young people. In modern-day societies tending to democracy and westernization, individuality is the prevailing feature of the hairstyle. Since art, sculpture, portraiture, and painting in the classical sense have disappeared, hairstyles in modern society are reflected mainly in products of the film and beauty industries, on television, and all sorts of celebrities and stars.

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55 The shorn hair is offered as a religious sacrifice.

56 Such as in medieval portraits of the Lord Jesus, both based on the Greek classic ideal. During the fourth and fifth centuries AD, Buddhist sculptors turned to the Hellenistic world as a matter of course for a visual conception of Buddha and quickly evolved several Hellenistic versions. In the popular Apollo version, Buddha has wavy hair. This type penetrated as far as Kashmir and Turkistan.

57 Samson and John the Baptist might have worn their hair this way. Rastafarians typically wear long dreadlocks, a hairstyle associated with the Ethiopian emperor Haile Selassie (1892–1975).

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Chapter 28

Hair in Forensic Medicine

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28

Synonyms

hair drug screening test, forensic hair analysis

Key Features

- Drugs, chemicals, and biological substances are stored in hair where they can be detected and measured.
- In hair samplings, the window of drug detection extends to months or even years.
- Collection is noninvasive, relatively easy to perform, and in forensic situations it may be achieved under close supervision to prevent adulteration or substitution.
- The sample size required for analysis is small and is easily stored at room temperature.
- Possible applications of hair analysis include diagnosis of drug abuse, poisoning and doping, evaluation of occupational exposure to toxics, evaluation of prenatal exposure to drugs, and monitoring of a patient's compliance with drug prescription.

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28.1 Introduction

Hair analysis for drugs and toxics has recently become very popular in several fields of medicine, including forensic and clinical toxicology and occupational medicine [2, 4, 8, 9] (Table 28.1).

Hair may in fact give a long-term history of drug intake and abuse as well as toxin exposure and therefore represents an unique substrate for forensic purposes. Collection is noninvasive, relatively easy to perform, and in forensic situations it may be achieved under the close supervision of law enforcement officers to prevent adulteration or substitution. The sample size required for analysis is small and is easily stored at room temperature.

The window of drug detection dramatically extends to months or even years, because long scalp hair may

Table 28.1 Drugs, chemical, and biological substances that can be detected and measured in hair [4]

• Amphetamines	Amphetamine Ephedrine Fenfluramine
• Anticonvulsants	
• Antidepressants and antipsychotics	
• Benzodiazepines	
• Cannabinoids	
• Chloroquine	
• Cocaine	
• Doping substances	
• Indinavir	
• Metals	Aluminum Arsenic Cadmium Chromium Copper Gold Iron Lead Manganese Mercury Nickel Selenium Silver Thallium Zinc
• Nicotine/Cotinine	
• Opiates	Codeine Heroin Morphine
• Pesticides and persistent organic pollutants	
• Polyamines	Putrescine Spermidine Spermine
• Sexual hormones	Estrone 17β-estradiol DHT Epitestosterone Testosterone Pregnenolone

provide retrospective information about the previous 5–7 years. Axillary and pubic hair can be utilized when the scalp hair is cut short.

28.2 History

Hair analysis for the detection of exposure to various substances can be done even years post-mortem. An historic example is the recent discovery that Napoleon's death was a result of arsenic poisoning. Measurement of the arsenic content along Napoleon's hair shaft permitted his assassination to be traced along a cosmetic and lethal phase. The cosmetic phase consisted of arsenic poisoning over time to weaken Napoleon, making the associated debility appear to be a natural illness. On May 3, 1821, at 5:30 p.m., the lethal phase was carried out: Napoleon was given Calomel (HgCl), a cathartic, and a popular orange-flavored drink called orgeat, which was flavored with the oil of bitter almonds. Together they formed mercury cyanide, which is lethal.

28.3 Pathophysiology of Incorporation of Substances into Hair

Drugs and toxics are incorporated into hair through three different modalities:

- Passive diffusion to the hair matrix from the blood and successive incorporation in the hair shaft during keratinization. Within the hair shaft drugs are bound to proteins, melanin or lipids. Correlation between blood and hair concentrations of the substances is not always linear and sometimes the distribution of the substances along the shaft does not correlate well with the time of exposure.
- Transfer to the formed hair shaft from sebum and sweat.
- Transfer to the formed shaft from the environment. External contamination may alter hair analysis and therefore decontamination processes are necessary to avoid false-positive results due to passive environmental exposure. Hair decontamination relies on the fact that substances transferred into hair by passive exposure are loosely bound to the surface of the shaft and can be removed by appropriate washing procedures.

28.4 Techniques of Analysis [8, 9]

28.4.1 Hair Sampling

Hair sampling is usually made from the vertex or from the pubis where hair is less contaminated by environmental and cosmetic factors. Hair should be cut close to its point of emergence from the skin to provide information about recent exposure. Hair analysis can be altered by cosmetic procedures such as dyeing, bleaching and permanent waving.

About 100–200 μg of hair is required for analysis. To determine the precise date or duration of intake, one can make use of the knowledge that the mean hair growth rate is 1 cm per month, cut the hair sample every 1–2 cm, and analyze the segments separately.

Samples can be stored for several months in a dry environment using paper or plastic envelopes.

28.4.2 Decontamination, Extraction, and Detection

Hair washing is important for removing external contaminants that are loosely bound to the hair surface. Washing with organic solvents and phosphate buffers permits the removal of both water-soluble and -insoluble substances.

Hair extraction procedures depend on the chemical characteristics of the compound being investigated. These include alkaline digestion, acidic extraction, and enzymatic digestion.

Hair analysis methods include immunoassays, gas chromatography, liquid chromatography, mass spectrometry, capillary electrophoresis, and infrared microscopy. Gas chromatography with mass spectrometry offers the best selectivity, sensitivity, and specificity for most substances.

28.5 Clinical Interpretation

Ruling out external contamination is a main issue. An important criterion for establishing whether active consumption/ingestion has occurred is the presence of both the substance and its metabolites within the sample. Since some drugs such as heroin and cocaine are labile molecules, which can be partially hydrolyzed within the hair fibers, cut-off ratios of metabolite to parent drug have been established (6-monoacetylmorphine:morphine >1.3; benzoylecgonine:cocaine >0.05).

28.6 Purposes of Hair Analysis

28.6.1 Forensic Investigations

28.6.1.1 Drug Abuse and Poisoning

Hair analysis permits the tracing of abuse of opiates, cocaine, amphetamines cannabinoids, nicotine, alcohol, and benzodiazepines.

28.6.1.2 Rape Cases

DNA typing can be easily performed on plucked hair and dandruff scales, which can be used to look for the DNA of aggressors in cases where the victims struggled to defend themselves [5].

28.6.2 Doping Controls

Although not yet approved by the International Olympic Committee (IOC) hair analysis is very useful for evaluating doping practices in professional athletes. Doping substances that can be detected in the hair include: clenbuterol, corticosteroids, ephedrine, methenolone, nandrolone metabolites, salbutamol, stanozolol, and testosterone.

The storage of both nandrolone and its metabolites (norandrosterone and noretiocholanolone) in hair samples permit discrimination of the intake of doping agents from the intake of other 19-norsteroids such as norandrostenedione and norandrostenediol, which are available in over the counter vitamin supplementations [6, 7].

28.6.3 Occupational Medicine

Hair analysis can be used to assess indoor hair pollution by organic chemicals and occupational exposure to toxic substances such as pesticides through inhalation or via the food chain [2].

Substances that can be traced include organochlorine pollutants, organophosphates, carbamates, and pyrethroides. Hair samples can also be utilized to evaluate environmental and occupational exposure of workers to pollutants (lead, nicotine) or metals (nickel, chromium). A strict correlation between mercury level in the hair and fish intake has been recently established.

28.6.4 Prenatal Exposure

Hair analysis can be applied clinically to document in utero exposure to drugs, and other toxic substances including nicotine and alcohol [3].

28.6.5 Patient's Compliance to Drug Prescription

Hair analysis is a useful tool to monitor treatment compliance in psychiatric, epileptic, and HIV-positive patients [1].

Another clinical application could be hormone analysis in hair shafts. The dosage of androgens in terminal scalp hair may provide a basis for predicting baldness: the ratio of testosterone: epitestosterone has been demonstrated to be significantly greater in the hair of balding fathers and their sons than in the hair of nonbalding control subjects [6].

28.7 Future Developments

New substances are constantly being measured and hair analysis has the potential for use in other fields of medicine.

Summary for the Clinician

Hair analysis is a necessary complement to blood and urine analysis in order to verify long-term and single exposure to drugs and poisons.
Sample collection is noninvasive and easy to perform under conditions that prevent adulteration and substitution.

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